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# Studies on Useful Protection of Functional Groups and Deprotection of Protecting Groups Using 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and Related Reactions

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## Chapter 1. General Introduction

2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (**1**) is one of the most important reagents in synthetic organic chemistry. DDQ was first synthesized in 1906 by Thiele and Günther.<sup>1)</sup> After that, numerous synthetic utilities have been developed for the dehydrogenation of hydroaromatic systems.<sup>2)</sup> Among the quinones possessing electron-withdrawing groups, tetrachloro-*p*-benzoquinone (chloranil) (**2**) and tetrachloro-*o*-benzoquinone (*o*-chloranil) (**3**) are often employed for dehydrogenation, however, DDQ is used most frequently (Figure 1-1). For instance, DDQ reacts 550 times faster than chloranil in the dehydrogenation of tetralin.<sup>2)</sup> For dehydrogenation by DDQ, hydride transfer mechanism has been proposed (Scheme 1-1).<sup>2,3)</sup> This mechanism includes a transfer of hydride to the quinone oxygen, followed by the transfer of a proton to the phenolate ion.

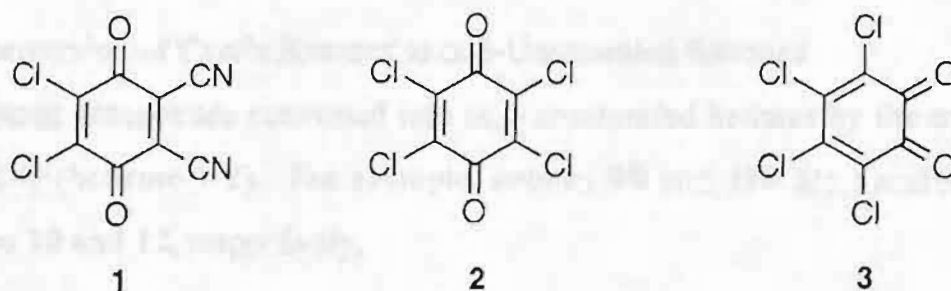
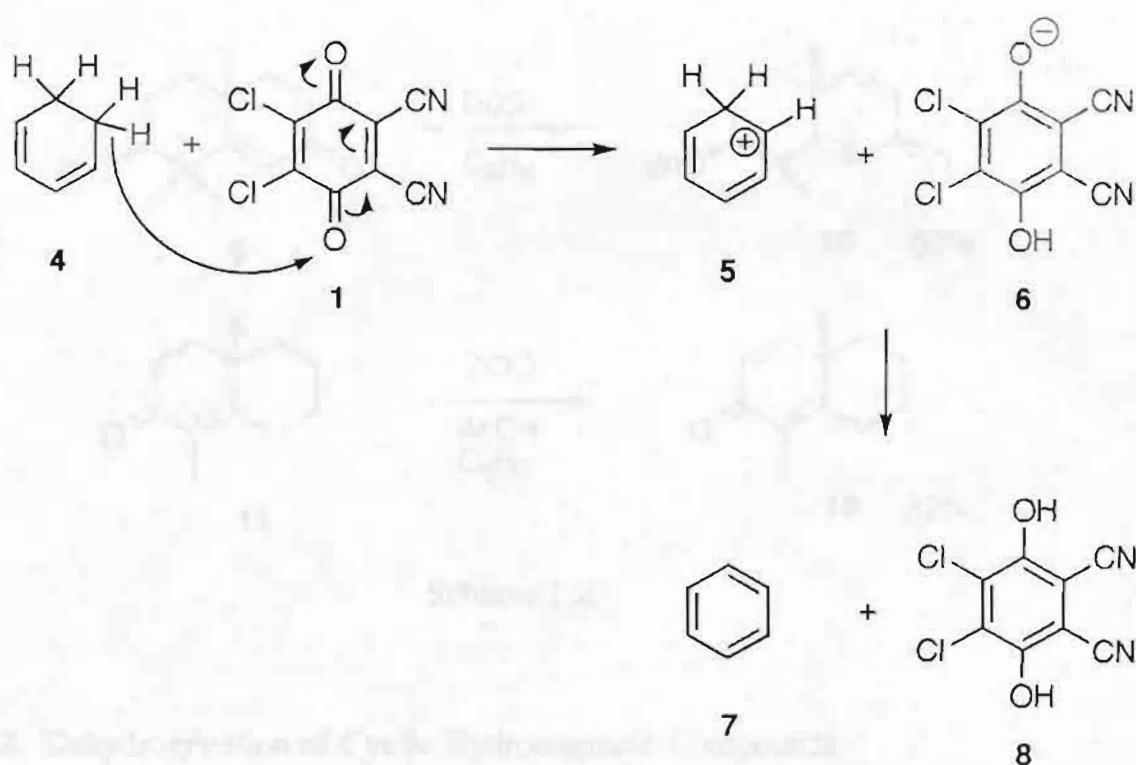


Figure 1-1.



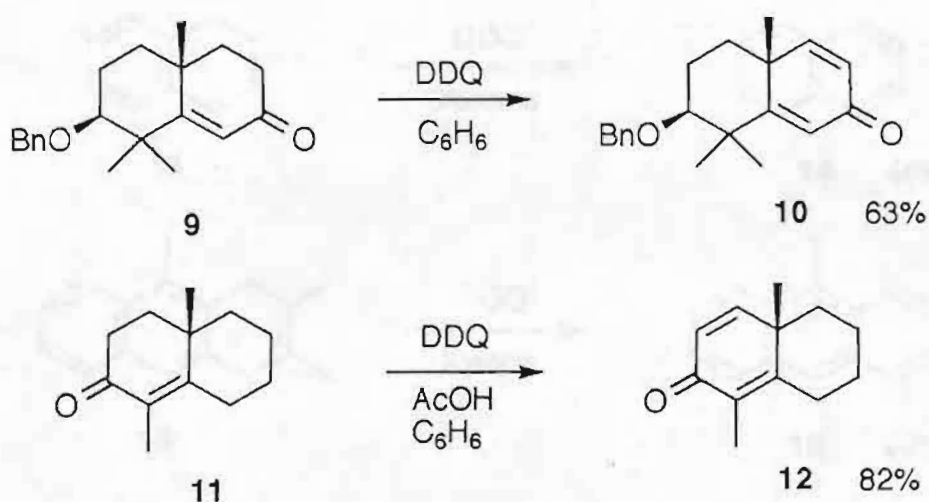


Scheme 1-1.

In the following sections, some representative reactions of DDQ are described.

#### 1-1. Conversion of Cyclic Ketones to $\alpha,\beta$ -Unsaturated Ketones

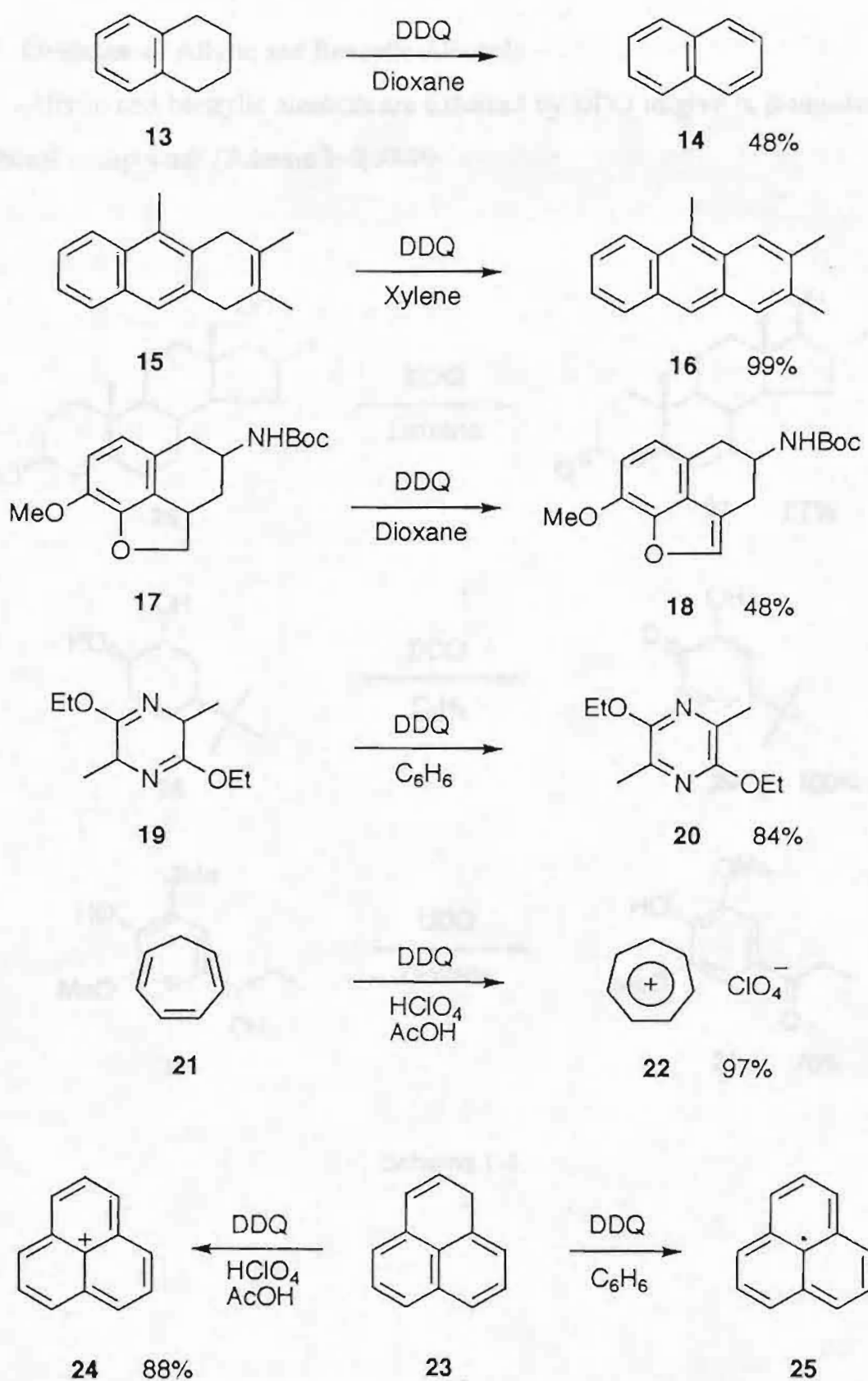
Cyclic ketones are converted into  $\alpha,\beta$ -unsaturated ketones by the treatment with DDQ (Scheme 1-2). For example, enones **9**<sup>4)</sup> and **11**<sup>5)</sup> are transformed to dienones **10** and **12**, respectively.



Scheme 1-2.

## 1-2. Dehydrogenation of Cyclic Hydroaromatic Compounds

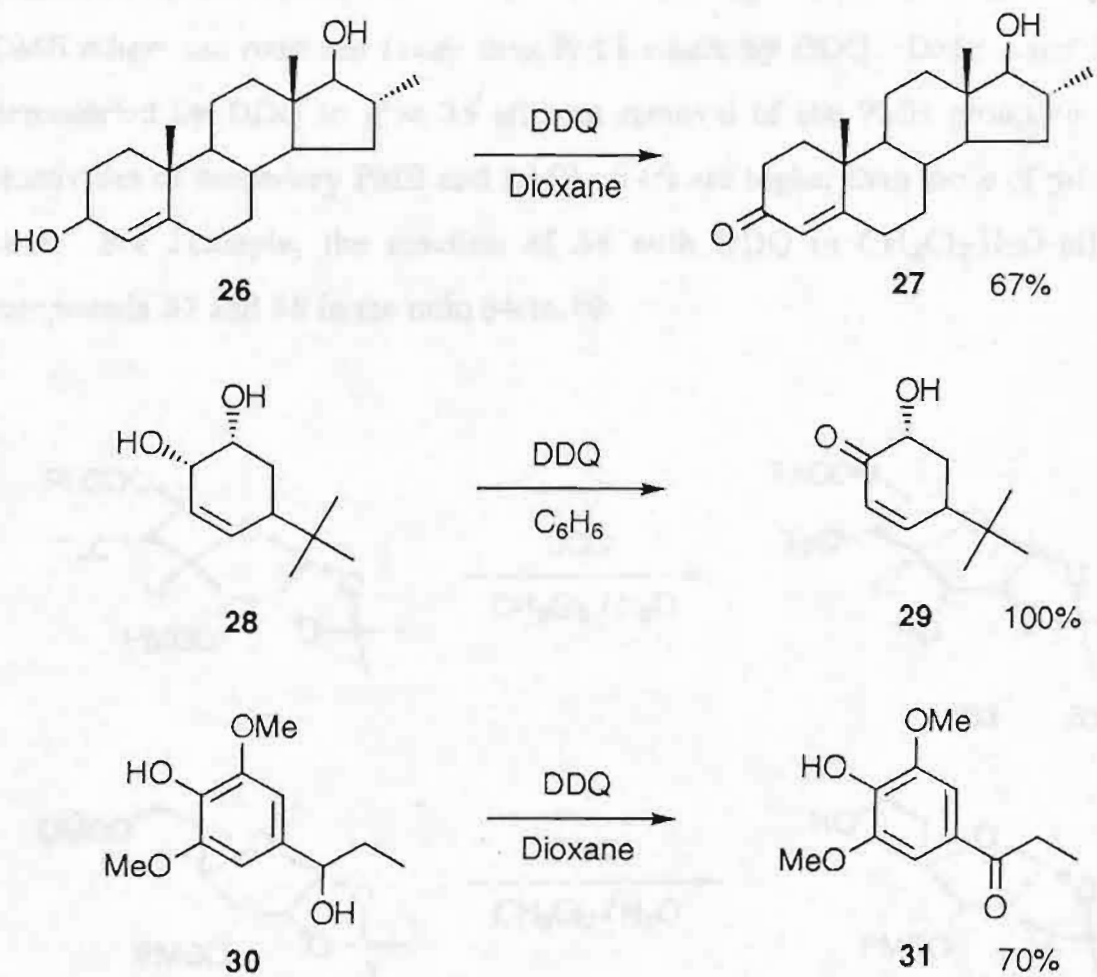
Cyclic hydroaromatic compounds such as **13**<sup>6)</sup> and **15**<sup>7)</sup> are dehydrogenated by DDQ to give aromatic compounds as shown in Scheme 1-3. DDQ is also useful for the synthesis of unsaturated heterocyclic compounds such as **18**<sup>8)</sup> and **20**.<sup>9)</sup> Synthesis of stable cations or radicals using DDQ is possible. Cycloheptatriene (**21**) is treated with DDQ and HClO<sub>4</sub> in acetic acid to give tropylium cation (**22**). Perinaphthalene (**23**) reacts with DDQ to give perinaphthyl radical (**25**), on the other hand, **23** reacted with DDQ and HClO<sub>4</sub> in acetic acid to form perinaphthyl cation (**24**).<sup>11)</sup>



Scheme 1-3.

### 1-3. Oxidation of Allylic and Benzylic Alcohols

Allylic and benzylic alcohols are oxidized by DDQ to give  $\alpha, \beta$ -unsaturated carbonyl compounds (Scheme 1-4).<sup>12-14)</sup>

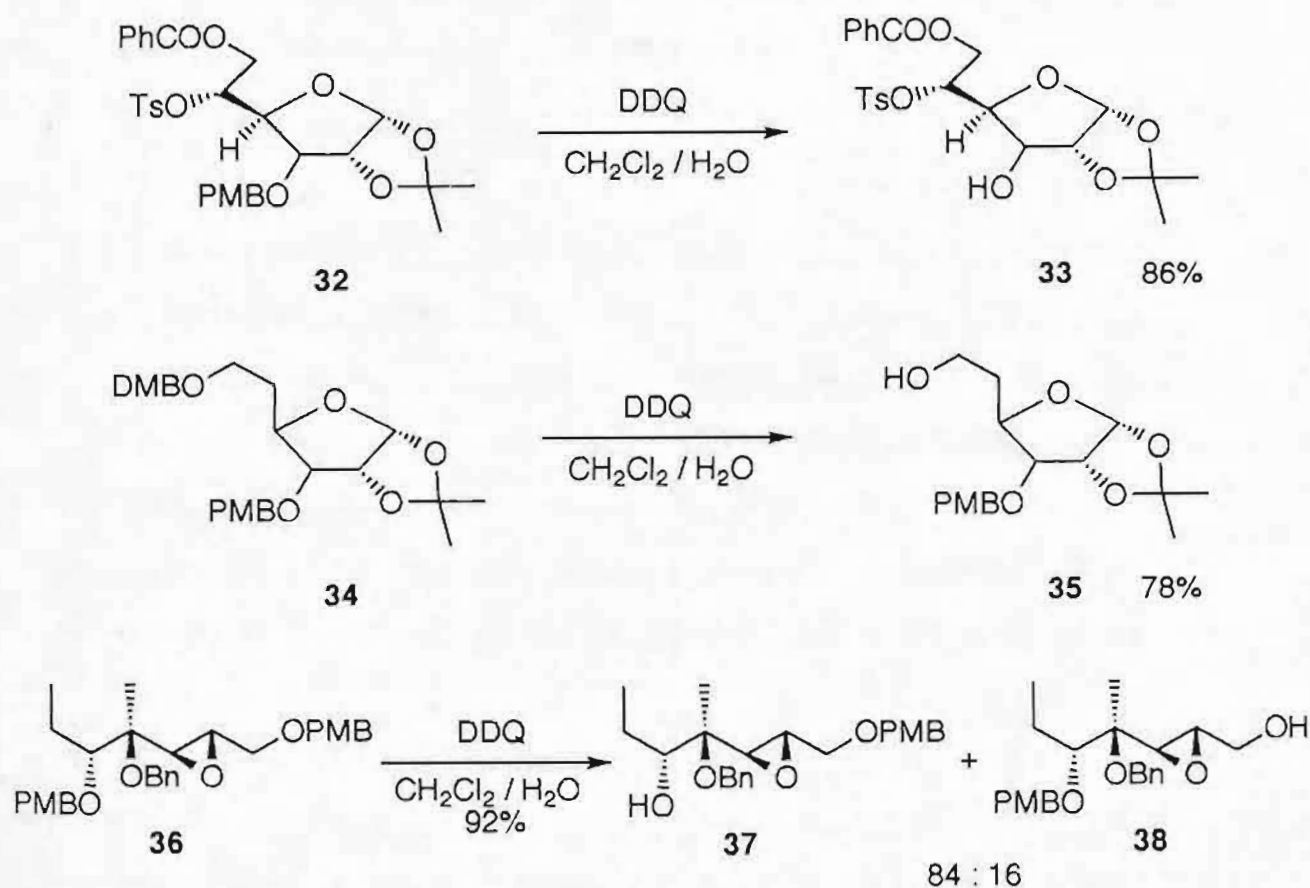


Scheme 1-4.



#### 1-4. Deprotection of *p*-Methoxybenzyl and 3,4-Dimethoxybenzyl Protecting Groups

*p*-Methoxybenzyl (PMB) and 3,4-Dimethoxybenzyl (DMB) groups are removed by the treatment with DDQ in  $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$  under neutral conditions (Scheme 1-5). Compound **32** is converted into **33** by the treatment with DDQ.<sup>15)</sup> DMB ethers are oxidized faster than PMB ethers by DDQ. DMB ether **34** is deprotected by DDQ to give **35** without removal of the PMB group.<sup>16)</sup> The reactivities of secondary PMB and DMB ethers are higher than those of primary ones. For example, the reaction of **36** with DDQ in  $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$  affords compounds **37** and **38** in the ratio 84:16.<sup>16)</sup>



Scheme 1-5.

This work is mainly concerned with the useful synthetic transformations using DDQ. In Chapters 2, 3, 4, and 5, the protection of the functional groups and the deprotection of the protecting groups using *a catalytic amount of DDQ* are reported. In Chapters 6 and 7, the deprotection of dithioacetals using *a stoichiometric amount of DDQ* is reported. In Chapters 8 and 9, the author describes the reactions of DDQ with heterocyclic compounds and cyclohexenyloxyboranes.

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## Chapter 2. Tetrahydropyranylation of Alcohols Catalyzed by DDQ

The protection of hydroxyl groups with 3,4-dihydro-2*H*-pyran (DHP) is a useful and representative method in modern synthetic chemistry.<sup>1)</sup> Many catalysts have been already proposed for this purpose. For the tetrahydropyranylation of alcohols, *p*-toluenesulfonic acid<sup>2)</sup> is the most common catalyst and seems to be superior to other catalysts such as hydrochloric acid,<sup>3)</sup> phosphoryl chloride,<sup>4)</sup> and boron trifluoride etherate.<sup>5)</sup> Owing to its strong acidity, however, *p*-toluenesulfonic acid is undesirable for highly acid-sensitive alcohols. Some less acidic catalysts, *i.e.*, pyridinium *p*-toluenesulfonate,<sup>6)</sup> bis(trimethylsilyl) sulfate,<sup>7)</sup> cobalt (III) chloride,<sup>8)</sup> and electrogenerated acid (EG acid)<sup>9)</sup> have been devised for this purpose. For example, pyridinium *p*-toluenesulfonate is a weaker acid (pH 3.0 in 1.0 M aqueous solution) than acetic acid (pH 2.4 in 1.0 M aqueous solution) (1 M = 1 mol dm<sup>-3</sup>).<sup>6)</sup> Recently, the tetrahydropyranylation of alcohols using magnesium bromide etherate, 2-(phenylsulfonyl)tetrahydropyran, and sodium hydrogencarbonate under mild basic conditions has been reported.<sup>10)</sup> In this chapter, it is reported that DDQ can efficiently catalyze the tetrahydropyranylation of alcohols.

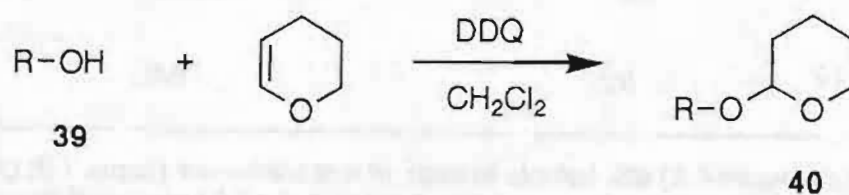


Figure 2-1.

Tetrahydropyranylation of dodecyl alcohol **39a** in several solvents was examined. As shown in Table 2-1, the best result was obtained in CH<sub>2</sub>Cl<sub>2</sub> (entries 1 and 2). In MeCN, the yield was slightly reduced (entry 6). The reactions in the other solvents proceeded much slowly (entries 3-5, and 7). Under aerobic conditions, the reaction was not disturbed (entry 2).

Table 2-1. Tetrahydropyranylation of Dodecyl Alcohol **39a** with DDQ in Various Solvents<sup>a)</sup>

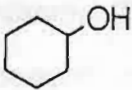
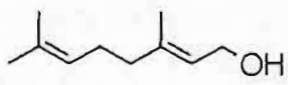
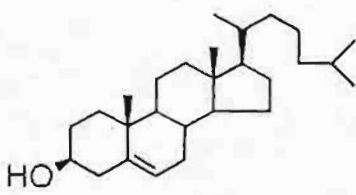
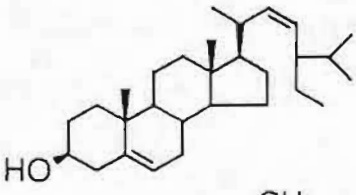
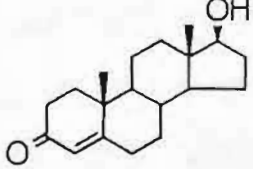
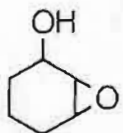
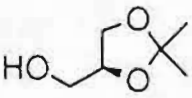
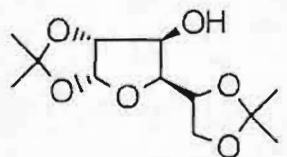
$\text{CH}_3(\text{CH}_2)_{11}\text{OH}$ <b>39a</b>		$\xrightarrow[\text{Solvent}]{\text{DDQ}}$	$\text{CH}_3(\text{CH}_2)_{11}\text{OTHP}$ <b>40a</b>
Entry	Solvent	Time / h	Yield / % <sup>b)</sup>
1	$\text{CH}_2\text{Cl}_2$	3	92
2 <sup>c)</sup>	$\text{CH}_2\text{Cl}_2$	3	92
3	$\text{C}_6\text{H}_6$	24	50
4	THF	24	19
5	Dioxane	24	0
6	MeCN	2	85
7	DMF	24	91

a) DDQ (0.1 mmol) was added to a mixture of alcohol **39a** (1.0 mmol) and DHP (1.5 mmol) in solvent (7.0 ml) at room temperature under nitrogen. b) Isolated yields. c) Under aerobic conditions.

Eleven alcohols **39a-k** were treated with DHP in the presence of a catalytic amount of DDQ in  $\text{CH}_2\text{Cl}_2$  to afford the corresponding tetrahydropyranyl (THP) ethers **40a-k**. The results are summarized in Table 2-2. It is worth pointing out that (1) protection using DDQ is effective for alcohols containing functional groups such as allylic hydroxyl, acetal, or epoxide (**39d**, **39i**, **39j**, **39k**), (2) THP ethers are obtained in excellent yields (> 90%) for a variety of alcohols, and (3) isolation of the product is remarkably simple.

The author conducted a brief examination of the mechanism of these reactions. The results are described in Chapter 5.

Table 2-2. Tetrahydropyranylation of Alcohols **39** with DDQ in CH<sub>2</sub>Cl<sub>2</sub>

	Alcohols <b>39</b>	Protection with DHP <sup>a)</sup>	
		Time / h	Yield <sup>b)</sup> of <b>40</b> / %
a	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> OH	3	92
b	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> OH	3	90
c		3	90
d		8	97 <sup>c)</sup>
e		6	100
f		6	98
g		6	100
h	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> OH	2	96
i		5	82
j		3	90
k		3	98 <sup>c)</sup>

a) DDQ (0.1 mmol) was added to a mixture of alcohol **39** (1 mmol) and DHP (1.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (7.0 ml) at room temperature under nitrogen. b) Isolated yields. c) 0.2 mmol of DDQ was used.



## Conclusions

A variety of hydroxyl compounds readily added to 3,4-dihydro-2*H*-pyran in the presence of a catalytic amount of DDQ to give high yields of the corresponding THP ethers. This method constitutes a new procedure for the preparation of THP ethers.

### General Procedure for Preparation of Alcohols 39 with DDQ Catalyzed by DDQ

DDQ (25 mg, 0.1 mmol) was added to a solution of 1-decanol (29a, 1.0 g, 10 mmol) and DDQ (1.25 mg, 0.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (7.0 ml). After stirring at room temperature for 2 h, the mixture was extracted with di-*n*-butyl ether. The extracts were washed with water, dried and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel) to give 40a (249 mg, 92%) (Table I, 11-13). 40a was obtained as a colorless oil with  $n_D^{20}$  1.432 and  $d_4^{20}$  0.812.

Compounds 40a-b and 40h were identified by comparison of their spectroscopic behavior (IR and  $^1\text{H}$  NMR) with those described in the literature.<sup>10,11</sup>

Analytical data of compounds 40a and 40j are as follows:  
40a: bp 87-89°C/0.5 Torr; IR (KBr) 1760, 911 and 819  $\text{cm}^{-1}$  (epoxy);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  = 0.90-1.10 (7H, m,  $\text{CH}_2$ ), 1.23-1.48 (9H, m,  $\text{CH}_2$  and  $\text{CH}_3$ ), 4.10 (2H, m,  $\text{CH}_2$ ), 4.54 (2  $\times$  1.24, 2  $\times$  1H, s, CH). Found: C, 68.49, H, 9.75%. Calcd for  $\text{C}_{11}\text{H}_{22}\text{O}_2$ : C, 68.00, H, 9.75%.

40j: bp 72-74°C/0.4 Torr; IR (KBr) ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  = 3.70 (s,  $\text{CH}_2$ ), 1.42

## Experimental

All boiling points are uncorrected. IR spectra were recorded on a Jasco IRA-2 spectrophotometer.  $^1\text{H}$  NMR spectra were measured on a JEOL JNM-FX 90Q (90 MHz) or a Hitachi R-24B (60 MHz) spectrometer using  $\text{Me}_4\text{Si}$  as an internal standard. Column chromatography was performed on Wakogel C-200 silica gel.  $\text{CH}_2\text{Cl}_2$  was distilled over  $\text{CaH}_2$  prior to use. DDQ was recrystallized from benzene-hexane.

General Procedure for Protection of Alcohols **39** with DHP Catalyzed by DDQ.

DDQ (23 mg, 0.1 mmol) was added to a mixture of 1-dodecanol (**39a**, 186 mg, 1.0 mmol) and DHP (126 mg, 1.5 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (7.0 ml). After stirring at room temperature for 3 h, the mixture was extracted with dichloromethane. The extracts were washed with water, dried and evaporated under reduced pressure. Column chromatography (benzene) of the residue gave the corresponding THP ether **40a** (249 mg, 92%) (Table 2-1). THP ethers **40e-g** and **40i-k** were obtained as an inseparable mixture of diastereomers at C-2'.

Compounds **40a-h** and **40k** were identified by comparison of their spectroscopic behaviors (IR and  $^1\text{H}$  NMR) with those described in the references.<sup>9-11)</sup>

Analytical data of compounds **40i** and **40j** are as follows.

**40i**: Bp 87-89 °C / 0.5 Torr; IR (Neat) 1260, 911, and 819  $\text{cm}^{-1}$  (epoxy);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  = 0.90-2.10 (12H, m,  $\text{CH}_2$ ), 3.12-3.68 (3H, m, CH and  $\text{CH}_2$ ), 4.16 (2H, m, CH), 4.80 and 4.94 (2 x 0.5H, 2 x br s, C2'-H). Found: C, 66.43; H, 9.17%. Calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_3$ : C, 66.64; H, 9.15%.

**40j**: Bp 72-74 °C / 0.4 Torr;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  = 1.37 (3H, s,  $\text{CH}_3$ ), 1.42

(3H, s, CH<sub>3</sub>), 1.37-1.98 (6H, m, CH<sub>2</sub>), 3.32-4.44 (7H, m, CH and CH<sub>2</sub>), and 4.64 (1H, br s, C2'-H). Found: C, 60.79; H, 9.49%. Calcd for C<sub>11</sub>H<sub>20</sub>O<sub>4</sub>: C, 61.09; H, 9.32%.

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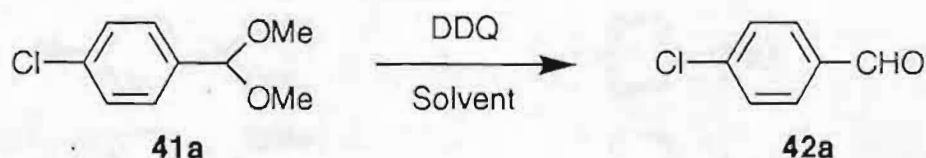
### Chapter 3. Deprotection of Acetals Catalyzed by DDQ

Conversion of acetals into aldehydes or ketones is one of the most important reactions in organic synthesis. This is normally accomplished by acid-catalyzed hydrolysis. For hydrolysis of dimethyl acetals, many protic acid catalysts such as hydrochloric acid,<sup>1)</sup> acetic acid,<sup>2)</sup> oxalic acid,<sup>3)</sup> tartaric acid,<sup>4)</sup> Dowex-50 (H<sup>+</sup>) resin,<sup>5)</sup> and *N*-hydroxy-benzenesulfonamide<sup>6)</sup> have been already proposed. Barton *et al.* have devised the oxidative cleavage of ketone ethylene acetals to ketones by trityl tetrafluoroborate.<sup>7)</sup>

Oikawa and Yonemitsu *et al.* reported that *p*-methoxybenzyl and 3,4-dimethoxybenzyl protecting groups of alcohols were removed by stoichiometric amounts of DDQ.<sup>8)</sup> In this chapter, a simple and efficient method for the transformation of acetals into the corresponding aldehydes or ketones by use of a catalytic amount of DDQ is reported.

First, the hydrolysis of *p*-chlorobenzaldehyde dimethyl acetal was examined in several solvents. As shown in Table 3-1, the best result was obtained in the case of MeCN-H<sub>2</sub>O (9:1). The reactions in other solvents such as CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O, Benzene-H<sub>2</sub>O, and THF-H<sub>2</sub>O proceeded much slowly. This reaction is only achieved in the presence of water. When water was not added, only a trace amount of the desired product was obtained (entry 5).

Table 3-1. Hydrolysis of *p*-Chlorobenzaldehyde Dimethyl Acetal by DDQ in Various Solvents<sup>a)</sup>



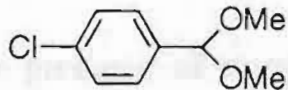
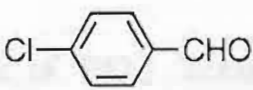
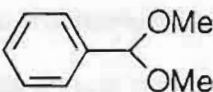
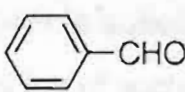
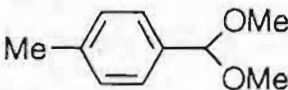
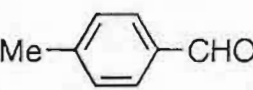
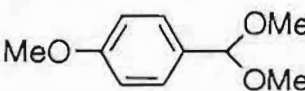
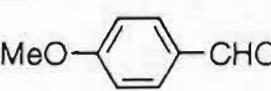
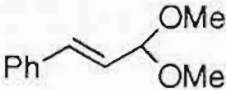
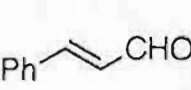
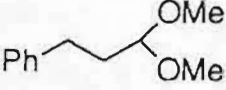
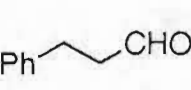
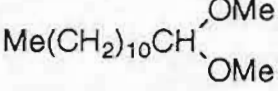
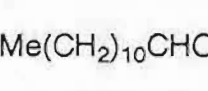
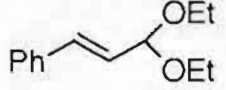
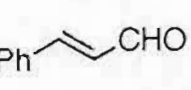
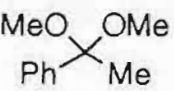
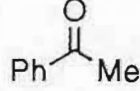
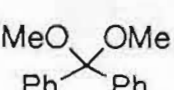
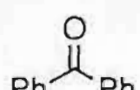
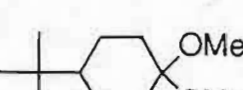
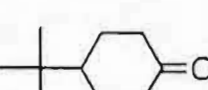
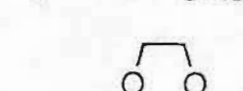

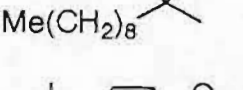
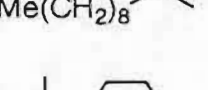
Entry	Solvent	Time / h	Yield % <sup>b)</sup>
1	MeCN-H <sub>2</sub> O (9:1)	1	92
2	CH <sub>2</sub> Cl <sub>2</sub> -H <sub>2</sub> O (9:1)	6	88
3	Benzene-H <sub>2</sub> O (9:1)	6	25
4	THF-H <sub>2</sub> O (9:1)	6	83
5	MeCN	1	4

a) DDQ (0.1 mmol) was added to a solution of *p*-chlorobenzaldehyde dimethyl acetal (1.0 mmol) in solvent (7.0 ml) at room temperature under nitrogen. b) Isolated yields.

Next, deprotection of various acetals catalyzed by DDQ was examined and the results are summarized in Table 3-2. In every case, the reaction proceeds smoothly at room temperature in aqueous acetonitrile to give the corresponding aldehydes or ketones in good yields. The hydrolysis of benzyl or allylic derivatives (entries 1-5) is faster than that of aliphatic ones (entries 6 and 7). This method can also be effective for ketone ethylene acetals as well as ketone dimethyl acetals (entries 12 and 13).

For the deprotection of acetals catalyzed by DDQ, protic acid, single electron transfer, and Lewis acid mechanisms have been reported.<sup>9,10)</sup> The author investigated the mechanism and the results are described in Chapter 5.

Table 3-2. Hydrolysis of Various Acetals by DDQ in MeCN-H<sub>2</sub>O (9:1)<sup>a)</sup>

Entry	Acetal <b>41</b>	Time / h	Product <b>42</b>	Yield % <sup>b)</sup>
1		1		92
2		1		75 <sup>c)</sup>
3		1		82
4		1		91
5		1		100
6		7		96
7		2		81
8		5		94
9		1		90
10		1		100
11		1		92
12		3		95
13		3		68 <sup>d,e)</sup>

a) DDQ (0.1 mmol) was added to a solution of the acetal (1.0 mmol) in MeCN-H<sub>2</sub>O (9:1) (7.0 ml) at room temperature under nitrogen. b) Isolated yields. c) Yield is low because of high volatility of benzaldehyde. d) DDQ (0.2 mmol) was used. e) The starting material (23%) was recovered.



## Conclusions

In the presence of a catalytic amount of DDQ, acetals were readily hydrolyzed to the corresponding aldehydes or ketones in aqueous MeCN. This method constitutes a new procedure for the deprotection of acetals.



## Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi I-3000 spectrophotometer.  $^1\text{H}$  NMR spectra were measured on a Hitachi R-24B (60 MHz) spectrometer using  $\text{Me}_4\text{Si}$  as an internal standard. Column chromatography was performed on Wakogel C-200 silica gel. DDQ was recrystallized from benzene-hexane. Acetals **41** were synthesized by the reported methods.<sup>11,12</sup> Compounds **42** were identified by comparison of the IR and  $^1\text{H}$  NMR spectra with those of commercially available samples.

### General Procedure for the Deprotection of Acetals **41** Catalyzed by DDQ.

DDQ (23 mg, 0.1 mmol) was added to a solution of *p*-chlorobenzaldehyde dimethyl acetal (187 mg, 1.0 mmol) in  $\text{MeCN-H}_2\text{O}$  (9:1) (7.0 ml). After stirring for 1 h at room temperature, the solvent was evaporated and the residue was chromatographed (benzene) on silica gel to give *p*-chlorobenzaldehyde (129 mg) in 92% yield; colorless needles, mp 47 °C (aqueous ethanol); IR (KBr) 1700  $\text{cm}^{-1}$  (CHO);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 7.50 (2H, d,  $J$  = 9.0 Hz, ArH), 7.83 (2H, d,  $J$  = 9.0 Hz, ArH), and 9.98 (1H, s, CHO).

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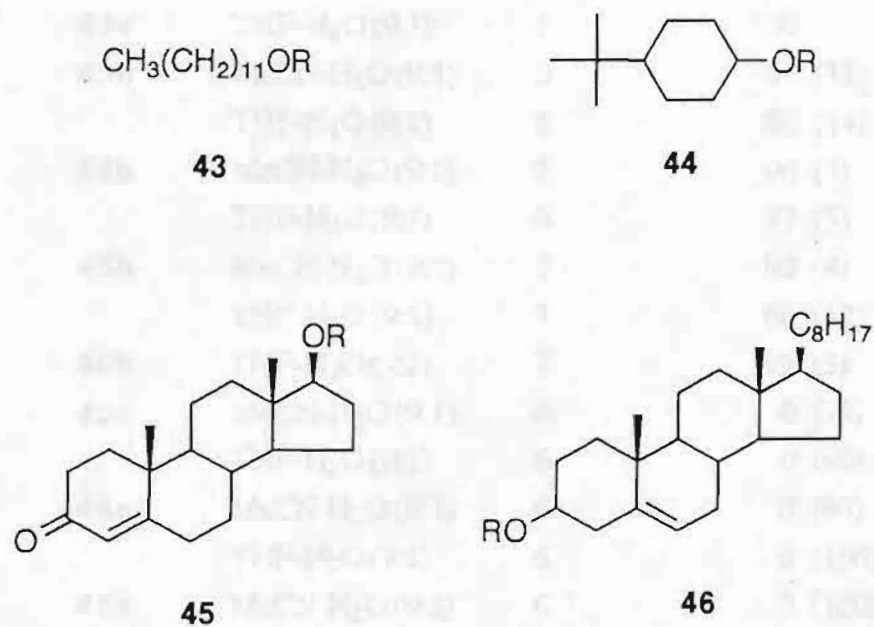
## Chapter 4. Deprotection of Silyl Ethers Catalyzed by DDQ

Silyl ethers as protecting groups for alcohols have been extensively used in recent synthetic works.<sup>1)</sup> Their popularity is due to their ease of formation and removal and their stability to a wide range of reagents. Among many silyl protecting groups, the most widely used ones are triethylsilyl (TES), *tert*-butyldimethylsilyl (TBDMS), and *tert*-butyldiphenylsilyl (TBDPS) ethers.<sup>2-4)</sup> A variety of methods have been developed for the removal of silyl groups. For example, hydrolysis using protic acids such as acetic acid are known. Owing to its strong acidity, protic acids are not undesirable for acid-sensitive substrates. As a less acidic reagent, fluorosilicic acid ( $\text{H}_2\text{SiF}_6$ ) has been proposed.<sup>5)</sup> As a unique reagent for deprotection of silyl ethers, tetra-*n*-butylammonium fluoride was devised,<sup>6)</sup> but fluoride ion in an aprotic solvent is a strong base.<sup>7)</sup> Recently, reductive cleavage of TBDMS ethers by diisobutylaluminium hydride has been reported by Corey *et al.*<sup>8)</sup> They also reported the use of  $\text{SiF}_4$  as a selective desilylating reagent.<sup>9)</sup> In this chapter, a new method for the cleavage of silyl ethers using a catalytic amount of DDQ is reported.

First, the hydrolysis of dodecyl TES ether in various solvents was examined. The results are summarized in Table 4-1. In MeCN- $\text{H}_2\text{O}$  (9:1) or THF- $\text{H}_2\text{O}$  (9:1), the reaction completed within 1 h at room temperature to give dodecyl alcohol in 93 or 97% yield, respectively. In  $\text{CH}_2\text{Cl}_2$ - $\text{H}_2\text{O}$  (19:1), the reaction was very slow. In benzene- $\text{H}_2\text{O}$  (19:1), the reaction did not occur (entries 1-4). This reaction is only achieved in the presence of water. When water was not added, most of dodecyl TES ether was recovered (entries 5 and 6). Next, deprotection of various TES ethers was examined. In every case, the reaction proceeded smoothly in MeCN- $\text{H}_2\text{O}$  or THF- $\text{H}_2\text{O}$  within 1 h to give the corresponding alcohols in quantitative yields (entries 7-11). The reactions of the other silyl ethers, TBDMS and TBDPS ethers, were also explored. The TBDMS ethers require 3-7 h to complete the

reaction (entries 12-18). The TBDMS group is less readily hydrolyzed than the TES group. TBDPS ethers did not react at all under these reaction conditions (entries 19-25). The selectivities of this reaction are the same as those described with protic acids, tetra-*n*-butylammonium fluoride, and SiF<sub>4</sub> methods.

The mechanism for the deprotection of silyl ethers is also discussed in Chapter 5.



a, R = TES; b, R = TBDMS; c, R = TBDPS; d, R = H

Figure 4-1.



Table 4-1. Deprotection of Various Silyl Ethers by DDQ in Several Solvents<sup>a)</sup>

Entry	Silyl ether	Solvent	Time / h	Yield / % <sup>b,c)</sup>
1	<b>43a</b>	MeCN-H <sub>2</sub> O (9:1)	1	93
2		THF-H <sub>2</sub> O (9:1)	1	97
3		CH <sub>2</sub> Cl <sub>2</sub> -H <sub>2</sub> O (19:1)	7	55 (45)
4		C <sub>6</sub> H <sub>6</sub> -H <sub>2</sub> O (19:1)	7	0 (96)
5		MeCN	1	19 (80)
6		THF	1	0 (71)
7	<b>44a</b>	MeCN-H <sub>2</sub> O (9:1)	1	100
8		THF-H <sub>2</sub> O (9:1)	1	100
9	<b>45a</b>	MeCN-H <sub>2</sub> O (9:1)	1	88
10		THF-H <sub>2</sub> O (9:1)	1	95
11 <sup>d)</sup>	<b>46a</b>	THF-H <sub>2</sub> O (9:1)	1	90
12	<b>43b</b>	MeCN-H <sub>2</sub> O (9:1)	6	65 (33)
13		THF-H <sub>2</sub> O (9:1)	6	86 (14)
14	<b>44b</b>	MeCN-H <sub>2</sub> O (9:1)	3	96 (4)
15		THF-H <sub>2</sub> O (9:1)	6	97 (3)
16	<b>45b</b>	MeCN-H <sub>2</sub> O (9:1)	7	92 (4)
17		THF-H <sub>2</sub> O (9:1)	7	88 (12)
18 <sup>d)</sup>	<b>46b</b>	THF-H <sub>2</sub> O (9:1)	7	93 (3)
19	<b>43c</b>	MeCN-H <sub>2</sub> O (9:1)	6	0 (92)
20		THF-H <sub>2</sub> O (9:1)	6	0 (96)
21	<b>44c</b>	MeCN-H <sub>2</sub> O (9:1)	6	0 (87)
22		THF-H <sub>2</sub> O (9:1)	6	0 (100)
23	<b>45c</b>	MeCN-H <sub>2</sub> O (9:1)	6	0 (100)
24		THF-H <sub>2</sub> O (9:1)	6	0 (100)
25 <sup>d)</sup>	<b>46c</b>	THF-H <sub>2</sub> O (9:1)	6	0 (100)

a) DDQ (0.1 mmol) in solvent (3.5 ml) was added to a solution of the silyl ether (1.0 mmol) in solvent (3.5 ml) under N<sub>2</sub> at room temp. b) Isolated yields. c) The figures in parentheses are the recovery of the starting materials. d) In MeCN-H<sub>2</sub>O (9:1), silyl ethers **46a-c** were not hydrolyzed at all because of their insolubility to the solvent.

## Conclusions

In the presence of a catalytic amount of DDQ, TES and TBDMS ethers were readily hydrolyzed to the corresponding alcohols in MeCN-H<sub>2</sub>O (9:1) or THF-H<sub>2</sub>O (9:1). TES ethers were cleaved to alcohols more easily than TBDMS ethers. TBDPS ethers were stable under these reaction conditions. This method constitutes a new procedure for deprotection of silyl ethers

### Typical Procedure for the Deprotection of Silyl Ethers Catalyzed by DDQ

To a solution of silyl ether (43a) (0.5 mmol, 0.15 g) in MeCN (10 mL) was added a solution of DDQ (2.5 mg, 0.01 mmol) in MeCN (1 mL). After stirring for 1 h at room temperature, the mixture was extracted with Et<sub>2</sub>O (10 mL) and the organic layer was washed with H<sub>2</sub>O (10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the alcohol (43a) (0.15 g, 100%) as a colorless solid. mp 34–35 °C (lit.<sup>1</sup> 34–35 °C). IR (KBr): 3400 (broad, OH), 2900 (C-H), 1600 (C=O), 1200 (C-O) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.2 (d, 2H, J = 8.0 Hz, H-6, H-7), 6.8 (d, 2H, J = 8.0 Hz, H-4, H-5), 5.2 (s, 2H, H-2, H-3), 4.8 (s, 2H, H-2, H-3), 3.8 (s, 3H, H-1), 2.5 (s, 3H, H-1), 1.5 (s, 3H, H-1). MS (m/z): 154 (M<sup>+</sup>), 136 (M<sup>+</sup>), 120 (M<sup>+</sup>).

## Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi I-3000 spectrophotometer.  $^1\text{H}$  NMR spectra were measured on a Hitachi R-24B (60 MHz) spectrometer using  $\text{Me}_4\text{Si}$  as an internal standard. Column chromatography was performed on Wakogel C-200 silica gel. DDQ was recrystallized from benzene-hexane. Silyl ethers **43a-46a**, **43b-46b**, and **43c-46c** were synthesized by the reported methods.<sup>2)</sup> Compounds **43d-46d** were identified by comparison of the IR and  $^1\text{H}$  NMR spectra with those of commercially available samples.

### Typical Procedure for the Deprotection of Silyl Ethers Catalyzed by DDQ

To a solution of dodecyl TES ether (**43a**) (300 mg, 1.0 mmol) in  $\text{MeCN-H}_2\text{O}$  (9:1) (3.5 ml) was added a solution of DDQ (23 mg, 0.1 mmol) in  $\text{MeCN-H}_2\text{O}$  (9:1) (3.5 ml). After stirring for 1 h at room temperature under  $\text{N}_2$ , the solvent was evaporated and the residue was chromatographed (benzene:ether = 2:1) on silica gel to give dodecyl alcohol (**43d**) (173 mg, 93%) as colorless crystalline solid, mp  $24^\circ\text{C}$  (aqueous ethanol) (*lit.*,<sup>10)</sup>  $24^\circ\text{C}$ ); IR (neat)  $3336\text{ cm}^{-1}$  (OH);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 0.92 (3H, t,  $J$  = 6.0 Hz,  $\text{CH}_3$ ), 1.10-1.78 (20H, br s,  $\text{CH}_2$ ), 1.89 (1H, s, OH), and 3.67 (2H, t,  $J$  = 6.0 Hz,  $\text{CH}_2$ ).



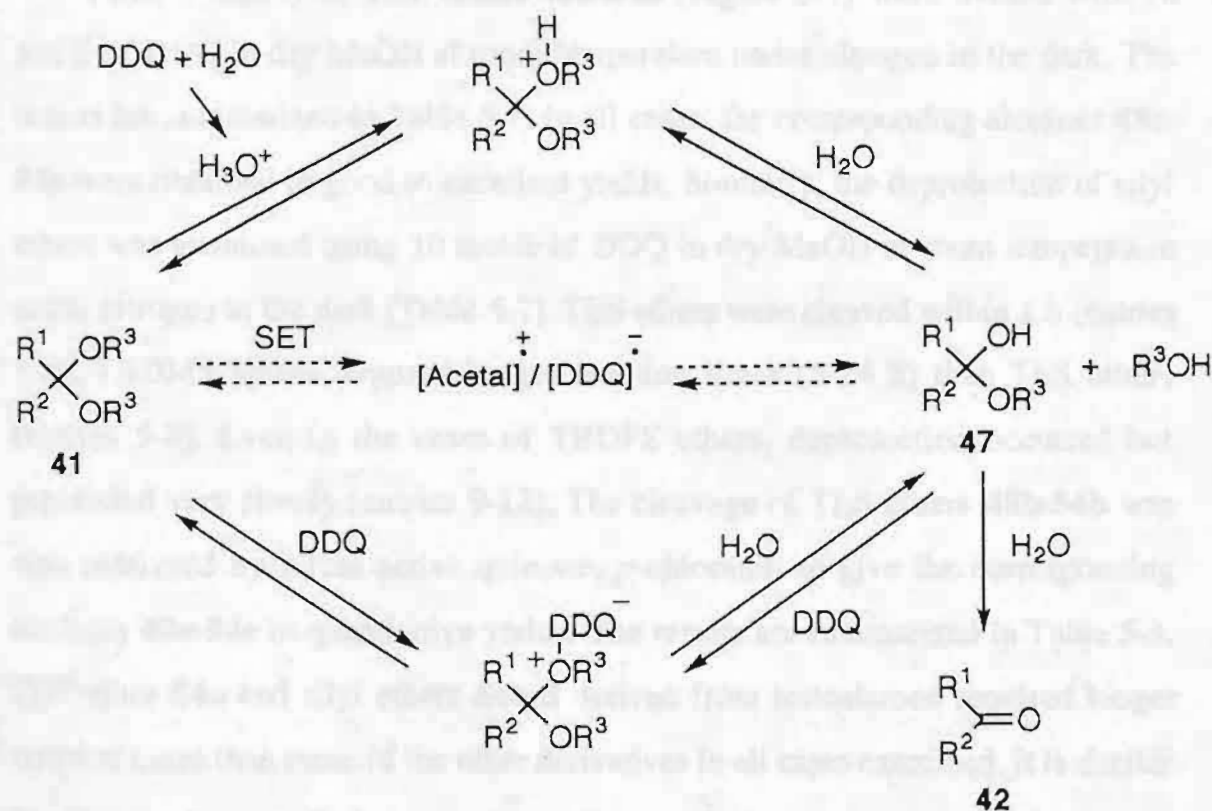
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- 10) H. Adkins and K. Folkers, *J. Am. Chem. Soc.*, **53**, 1095 (1931).



Chapter 5. Deprotection of Tetrahydropyranyl and Silyl Ethers Catalyzed by Various  $\pi$ -Acceptors

In Chapters 3 and 4, it was reported that acetals and silyl ethers were deprotected by a catalytic amount of DDQ in aqueous MeCN.<sup>1-5)</sup> Oku *et al.* also reported the similar cleavage of acetals and silyl ethers catalyzed by DDQ in aqueous ethyl acetate.<sup>6)</sup> They pointed out that acidic materials were produced by the reaction of DDQ with water under wet conditions. Furthermore, they reported that DDQ might act as a Lewis acid (Scheme 5-1). Iranpoor *et al.* have reported the ring opening reaction of epoxides with alcohols in the presence of a catalytic amount of DDQ *via* a SET mechanism.<sup>7)</sup>

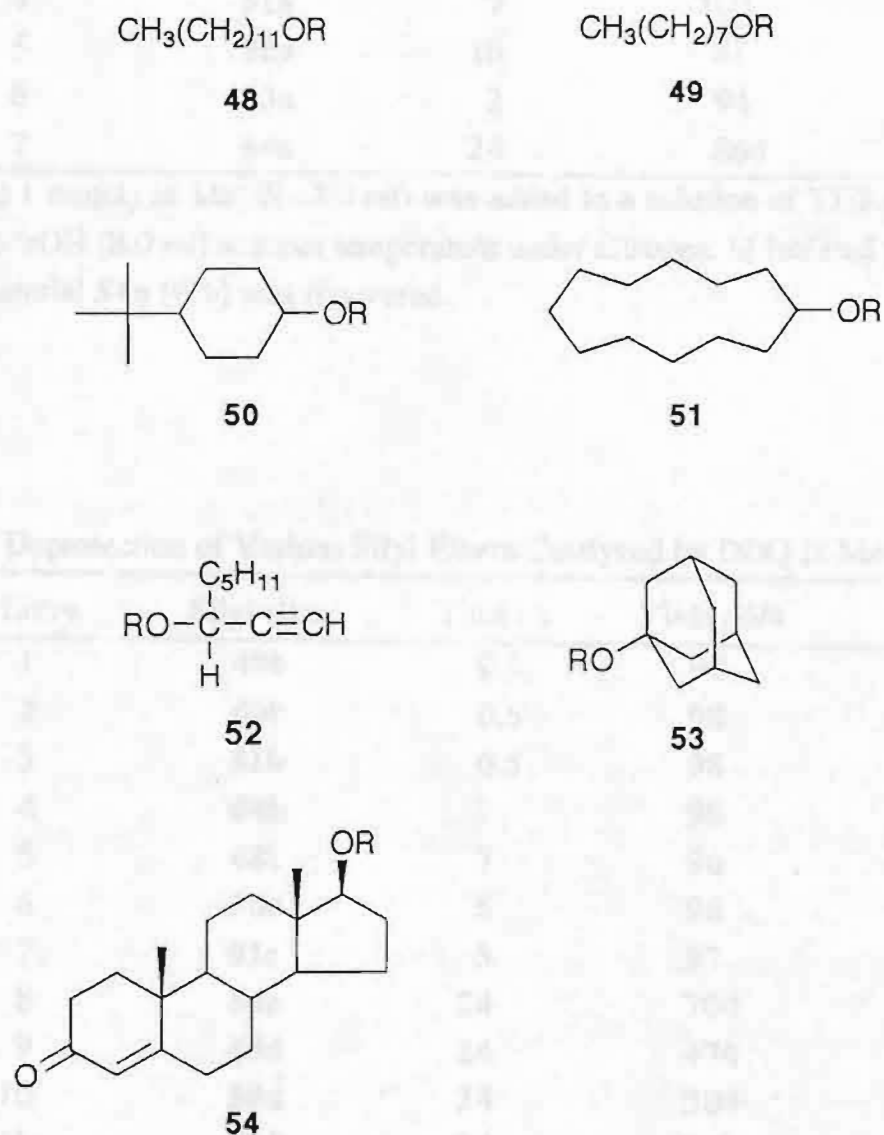


Scheme 5-1.

In connection with DDQ, tetracyanoethylene (TCNE) was reported to catalyze substrate-specific rearrangement, acetonidation,<sup>8a)</sup> alcoholysis of epoxides,<sup>8b)</sup> Mukaiyama aldol reaction of acetals,<sup>8c)</sup> and esterification and transesterification of carboxylic acids.<sup>8d)</sup> Dicyanoketene acetals were also reported to catalyze monothioacetalization of acetals,<sup>9a)</sup> alcoholysis of epoxides,<sup>9b)</sup> and tetrahydropyranylation of alcohols.<sup>9c)</sup> Although many examples<sup>10-13)</sup> catalyzed by  $\pi$ -acceptors are known, the mechanisms of these reactions are still unclear. The author examined the mechanisms of the deprotection of THP ethers and silyl ethers in the presence of a catalytic amount of DDQ in dry MeOH in order to avoid the hydrolysis of acceptors by water. In this chapter, the results of the deprotection catalyzed by various  $\pi$ -acceptors as well as DDQ in dry MeOH is described.

First, a variety of THP ethers **48a-54a** (Figure 5-1) were treated with 10 mol% of DDQ in dry MeOH at room temperature under nitrogen in the dark. The results are summarized in Table 5-1. In all cases, the corresponding alcohols **48e-54e** were obtained in good to excellent yields. Similarly, the deprotection of silyl ethers was examined using 10 mol% of DDQ in dry MeOH at room temperature under nitrogen in the dark (Table 5-2). TES ethers were cleaved within 1 h (entries 1-4). TBDMS ethers required longer reaction times (5-24 h) than TES ethers (entries 5-8). Even in the cases of TBDPS ethers, deprotection occurred but proceeded very slowly (entries 9-12). The cleavage of TES ethers **48b-54b** was also catalyzed by a less active quinone, *p*-chloranil, to give the corresponding alcohols **48e-54e** in quantitative yields. The results are summarized in Table 5-3. THP ether **54a** and silyl ethers **54b-d** derived from testosterone required longer reaction times than those of the other derivatives in all cases examined. It is similar to the tendency of deprotection promoted by protic acids such as *p*-toluenesulfonic acid (*p*-TsOH) and pyridinium *p*-toluenesulfonate (PPTS). For example, the cleavage of TBDMS ether **54c** catalyzed by PPTS in MeOH

proceeded very slowly (24 h, 2%), while the deprotection of the other TBDMS ethers **48c**, **50c**, and **51c** was completed within 24 h.



**a**, R = THP; **b**, R = TES; **c**, R = TBDMS; **d**, R = TBDPS; **e**, R = H

Figure 5-1.



Table 5-1. Deprotection of Various THP Ethers Catalyzed by DDQ in MeOH<sup>a)</sup>

Entry	THP ether	Time / h	Yield / % <sup>b)</sup>
1	<b>48a</b>	7	85
2	<b>49a</b>	10	90
3	<b>50a</b>	4	91
4	<b>51a</b>	7	100
5	<b>52a</b>	10	81
6	<b>53a</b>	2	94
7	<b>54a</b>	24	86 <sup>c)</sup>

a) DDQ (0.1 mmol) in MeOH (2.0 ml) was added to a solution of THP ether (1.0 mmol) in MeOH (8.0 ml) at room temperature under nitrogen. b) Isolated yields. c) Starting material **54a** (6%) was recovered.

Table 5-2. Deprotection of Various Silyl Ethers Catalyzed by DDQ in MeOH<sup>a)</sup>

Entry	Silyl ether	Time / h	Yield / % <sup>b)</sup>
1	<b>48b</b>	0.5	90
2	<b>50b</b>	0.5	98
3	<b>51b</b>	0.5	98
4	<b>54b</b>	1	98
5	<b>48c</b>	7	96
6	<b>50c</b>	5	96
7	<b>51c</b>	5	97
8	<b>54c</b>	24	70 <sup>c)</sup>
9	<b>48d</b>	24	47 <sup>d)</sup>
10	<b>50d</b>	24	28 <sup>e)</sup>
11	<b>51d</b>	24	31 <sup>f)</sup>
12	<b>54d</b>	24	2 <sup>g)</sup>

a) DDQ (0.1 mmol) in MeOH (2.0 ml) was added to a solution of silyl ether (1.0 mmol) in MeOH (8.0 ml) at room temperature under nitrogen. b) Isolated yields. c) Starting material **54c** (23%) was recovered. d) Starting material **48d** (50%) was recovered. e) Starting material **50d** (70%) was recovered. f) Starting material **51d** (67%) was recovered. g) Starting material **54d** (98%) was recovered.



Table 5-3. Deprotection of Various TES Ethers Catalyzed by *p*-Chloranil in MeOH<sup>a</sup>

Entry	TES ether	Time / h	Yield / % <sup>b</sup>
1	<b>48b</b>	3	95
2	<b>49b</b>	2	91
3	<b>50b</b>	3	100
4	<b>51b</b>	4	100
5	<b>52b</b>	2	89
6	<b>53b</b>	5	98
7	<b>54b</b>	24	100

a) *p*-Chloranil (0.05 mmol) in MeOH (2.0 ml) was added to a solution of TES ether (1.0 mmol) in MeOH (8.0 ml) at room temperature under nitrogen. b) Isolated yields.

Next, the cleavage of dodecyl TES ether **48b** using various  $\pi$ -acceptors was examined. The results are summarized in Table 5-4. The deprotection using strong acceptors possessing higher reduction potentials proceeded more rapidly. When DDQ was used, the deprotection proceeded most easily in the series of examined quinones (entry 1). The reaction occurred in the cases of the polyhalogenated quinones, *i.e.*, *o*-chloranil (**3**), 2,3,5,6-tetrafluoro-*p*-benzoquinone (**55**) (*p*-fluoranil), *p*-chloranil (**2**), and 2,3,5,6-tetrabromo-*p*-benzoquinone (**56**) (*p*-bromanil) (entries 2-5). The presence of the cyano group is not essential for the activity of acceptors. *p*-Benzoquinone (**57**) did not catalyze the reaction because of the low reduction potential (entry 6). When 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinodimethane (**58**) (TCNQF<sub>4</sub>) was used, the reaction proceeded most rapidly among the examined quinodimethanes **58-61** (entries 7-10). 11,11,12,12-Tetracyano-2,6-naphthoquinodimethane (**59**) has less activity than 7,7,8,8-tetracyanoquinodimethane (**60**) (TCNQ) in spite of the higher reduction potential compared to that of TCNQ (entries 8 and 9). 2,5-Dimethyl-7,7,8,8-tetracyanoquinodimethane (**61**) required longer reaction time than TCNQ (entries

9 and 10). Activity of TCNE (**62**) is almost comparable to those of DDQ and TCNQF<sub>4</sub>, although its reduction potential is not so high (entries 1, 7, and 11). In the case of 2,4,7-trinitrofluorenylidene malononitrile (**64**), the reaction did not proceed although the reduction potential is almost the same as that of *p*-chloranil (entries 4 and 13). Low activity of compounds **59**, **61**, and **64** could be attributed to the high stabilities of acceptors in MeOH. 1,2,4,5-Tetracyanobenzene (**66**), 9,10-dicyanoanthracene (**67**), 1,4-dicyanobenzene (**68**), and 1,4-dinitrobenzene (**69**) were not effective for deprotection because of their low reduction potentials (entries 15-18).

Table 5-4. Deprotection of Dodecyl TES Ether **48b** by a Catalytic Amount of Various  $\pi$ -Acceptors in MeOH

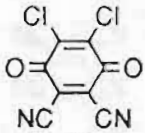
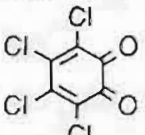
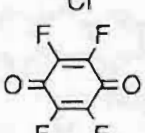
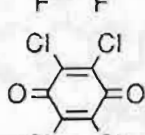
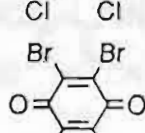
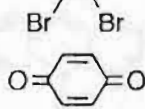
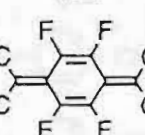
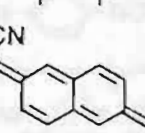
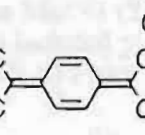
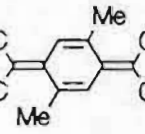
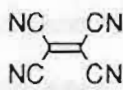
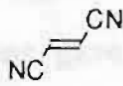
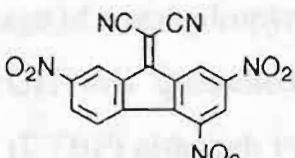
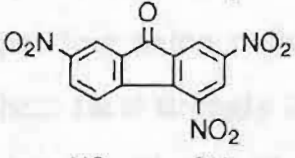
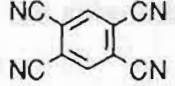
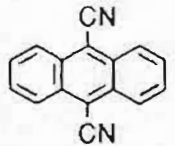

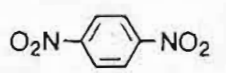
Entry	$\pi$ -Acceptor <sup>a)</sup>	$E_{\text{red}} / V^b)$	Time/ h	Yield of <b>48e</b> / % <sup>c)</sup>
1		<b>1</b> 0.59 <sup>d)</sup>	0.5	90
2		<b>3</b> 0.14 <sup>e)</sup>	3	88
3		<b>55</b> -0.04 <sup>e)</sup>	3	83
4		<b>2</b> 0.01 <sup>e)</sup>	3	95
5		<b>56</b> 0.00 <sup>e)</sup>	3	88
6		<b>57</b> -0.50 <sup>e)</sup>	24	0
7		<b>58</b> 0.53 <sup>d)</sup>	0.5	84
8		<b>59</b> 0.20 <sup>f)</sup>	24	86
9		<b>60</b> 0.13 <sup>f)</sup>	2	92
10		<b>61</b> 0.02 <sup>f)</sup>	24	92



Table S-4 (continued).

Entry	$\pi$ -Acceptor <sup>a)</sup>	$E_{\text{red}} / \text{V}^{\text{b)}$	Time/h	Yield of <b>48e</b> / % <sup>c)</sup>
11		<b>62</b> 0.15 <sup>d)</sup>	0.5	91
12		<b>63</b> - 2.03 <sup>g)</sup>	24	0
13		<b>64</b> 0.02 <sup>h)</sup>	24	0
14		<b>65</b> - 0.43 <sup>h)</sup>	24	0
15		<b>66</b> - 0.66 <sup>i)</sup>	24	0
16		<b>67</b> - 0.89 <sup>i)</sup>	24	0
17		<b>68</b> - 1.60 <sup>j)</sup>	24	0
18		<b>69</b> - 0.68 <sup>j)</sup>	24	0

a) Acceptor (0.1 mmol) in MeOH (8.0 ml) was added to a solution of TES ether **52b** (1.0 mmol) in MeOH (2.0 ml) at room temperature under nitrogen. b) V vs. SCE in MeCN. c) Isolated yields. d) From ref. 25. e) From ref. 26. f) From ref. 27. g) From ref. 28. h) From ref. 29. i) From ref. 30. j) From ref. 31.



To elucidate the deprotection mechanism, acid concentration of the solution of representative acceptors, *i.e.*, DDQ, *p*-chloranil, TCNQ, and TCNQF<sub>4</sub>, was measured in dry MeOH using a pH meter at room temperature under nitrogen. The results are shown in Figure 5-2, suggesting the presence of acidic medium developed during the reactions. The author compared both the results of the deprotection in the presence of acceptors and sulfuric acid. The reactions of **48a**, carried out in the presence of sulfuric acid under identical conditions in concentration of protons, gave almost the same results as the acceptor-promoted reactions. Cleavage of tetrahydropyranyl (THP) ether **48a** catalyzed by DDQ or TCNQF<sub>4</sub> in MeOH was quenched by adding 4 equivalents of 2,6-di-*tert*-butylpyridine<sup>14)</sup> (DTBP) although these acceptors reacted with DTBP slowly to give the corresponding anion radicals in MeCN when analyzed by UV-VIS spectroscopy. These facts strongly suggest that the deprotection is promoted by protons produced in the solvents.<sup>15)</sup>

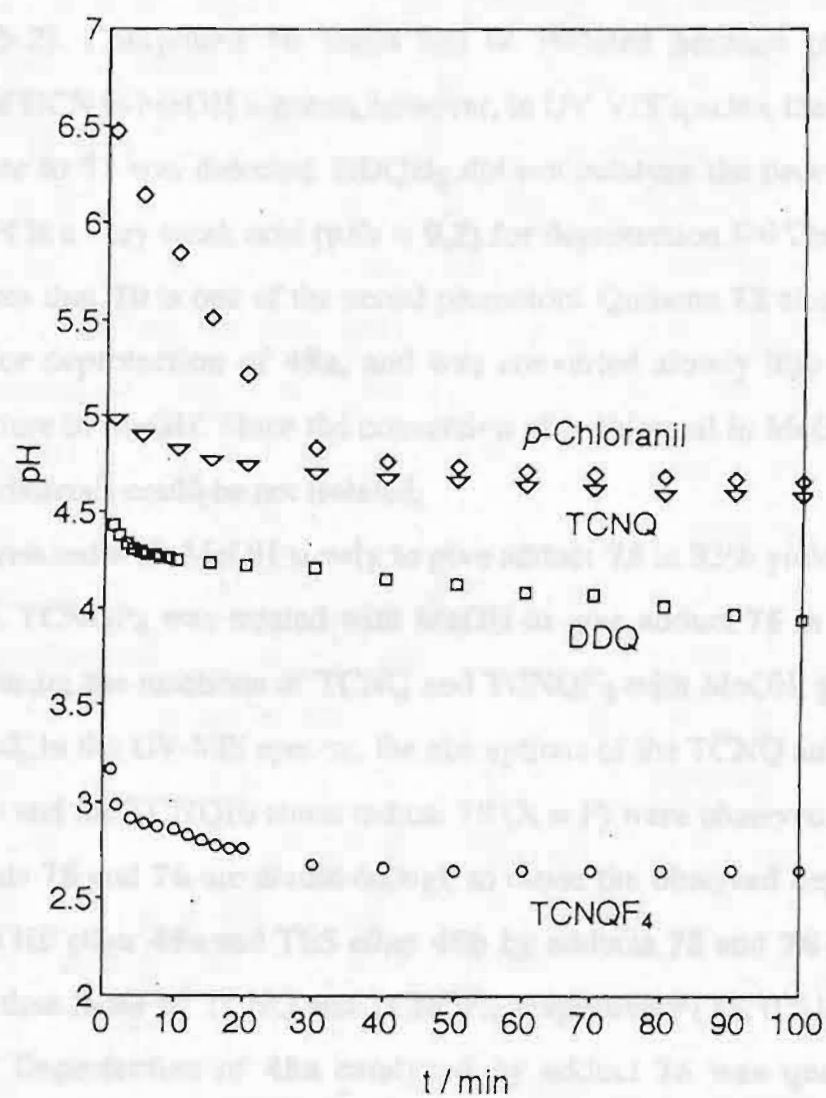
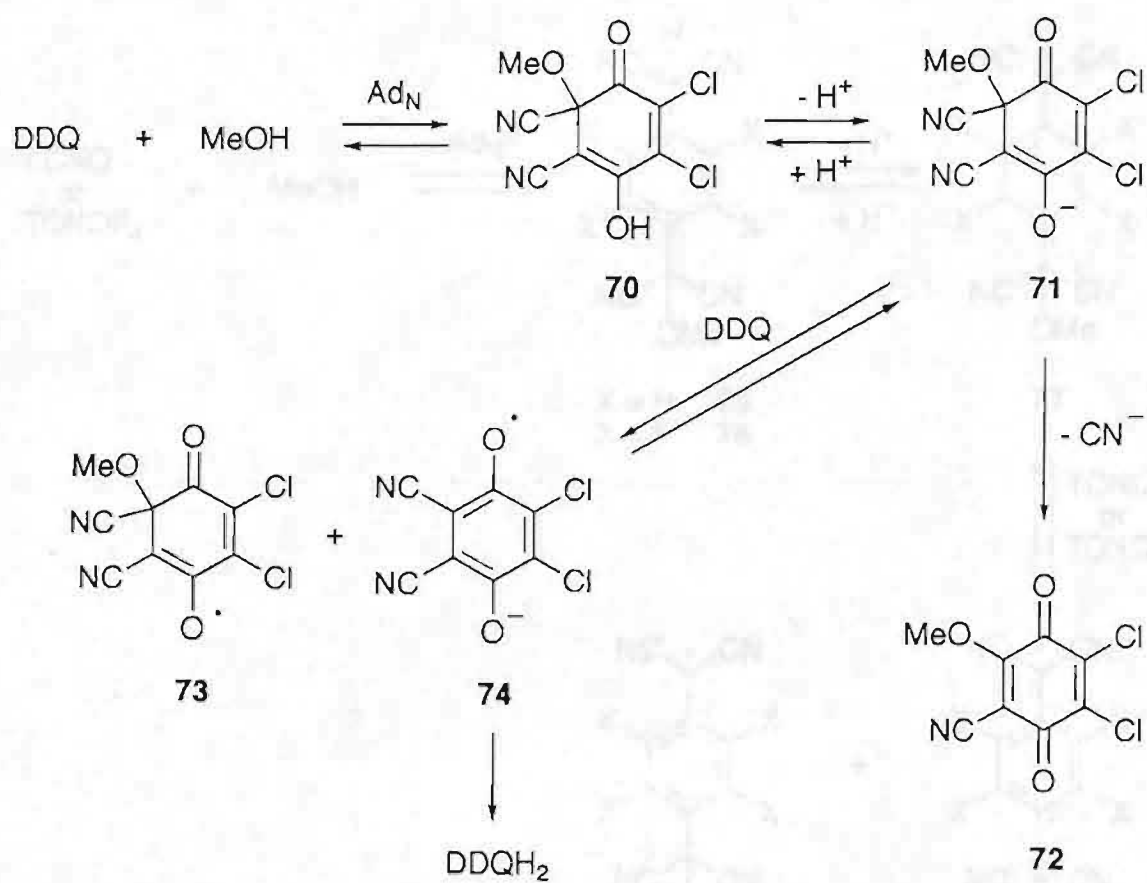


Figure 5-2. Plots of pH vs. time for the solution of various  $\pi$ -acceptors in MeOH. Concentrations of acceptors; DDQ ( $1.0 \times 10^{-2} \text{ mol dm}^{-3}$ ), *p*-chloranil ( $5.0 \times 10^{-3} \text{ mol dm}^{-3}$ ), TCNQ ( $1.0 \times 10^{-3} \text{ mol dm}^{-3}$ ), and TCNQF<sub>4</sub> ( $1.0 \times 10^{-2} \text{ mol dm}^{-3}$ ).

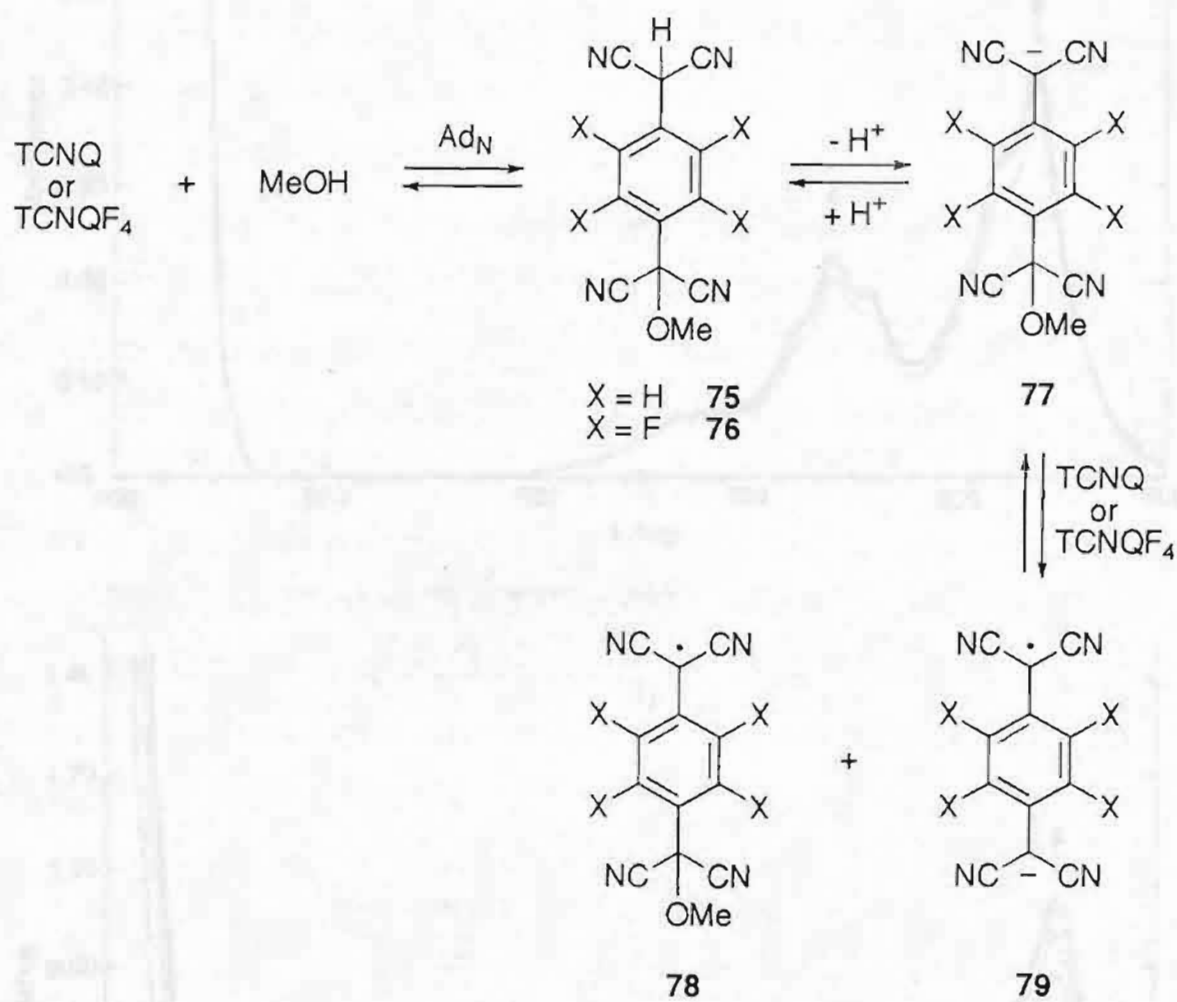
When DDQ was treated with MeOH, 2,3-dichloro-5-cyano-6-methoxy-*p*-benzoquinone (**72**)<sup>16)</sup> (14%) and 2,3-dichloro-5,6-dicyanohydroquinone (DDQH<sub>2</sub>) (20%) were isolated together with a large amount of the recovered DDQ after 48 h (Scheme 5-2). Compound **70** could not be isolated because of the easy elimination of HCN in MeOH solution, however, in UV-VIS spectra, the absorption at 465 nm due to **71** was detected. DDQH<sub>2</sub> did not catalyze the deprotection of **48a** and HCN is a very weak acid ( $pK_a = 9.2$ ) for deprotection.<sup>17a)</sup> Therefore, the author deduces that **70** is one of the actual promoters. Quinone **72** also possessed an activity for deprotection of **48a**, and was converted slowly into the acidic complex mixture in MeOH. Since the conversion of *p*-chloranil in MeOH was too slow, acidic materials could be not isolated.

TCNQ reacted with MeOH slowly to give adduct **75** in 33% yield after 96 h (Scheme 5-3). TCNQF<sub>4</sub> was treated with MeOH to give adduct **76** in 94% yield after 48 h. During the reactions of TCNQ and TCNQF<sub>4</sub> with MeOH, green color was developed. In the UV-VIS spectra, the absorptions of the TCNQ anion radical **79** ( $X = H$ )<sup>18)</sup> and the TCNQF<sub>4</sub> anion radical **79** ( $X = F$ ) were observed (Figure 5-3). Compounds **75** and **76** are acidic enough to cause the observed deprotection. Cleavage of THP ether **48a** and TES ether **48b** by adducts **75** and **76** proceeded more rapidly than those by TCNQ and TCNQF<sub>4</sub>, respectively (**75**, 0.5 h, 93%; **76**, 0.5 h, 90%). Deprotection of **48a** catalyzed by adduct **76** was quenched by adding 4 equivalents of DTBP.<sup>14)</sup>



Scheme 5-2.





Scheme 5-3.

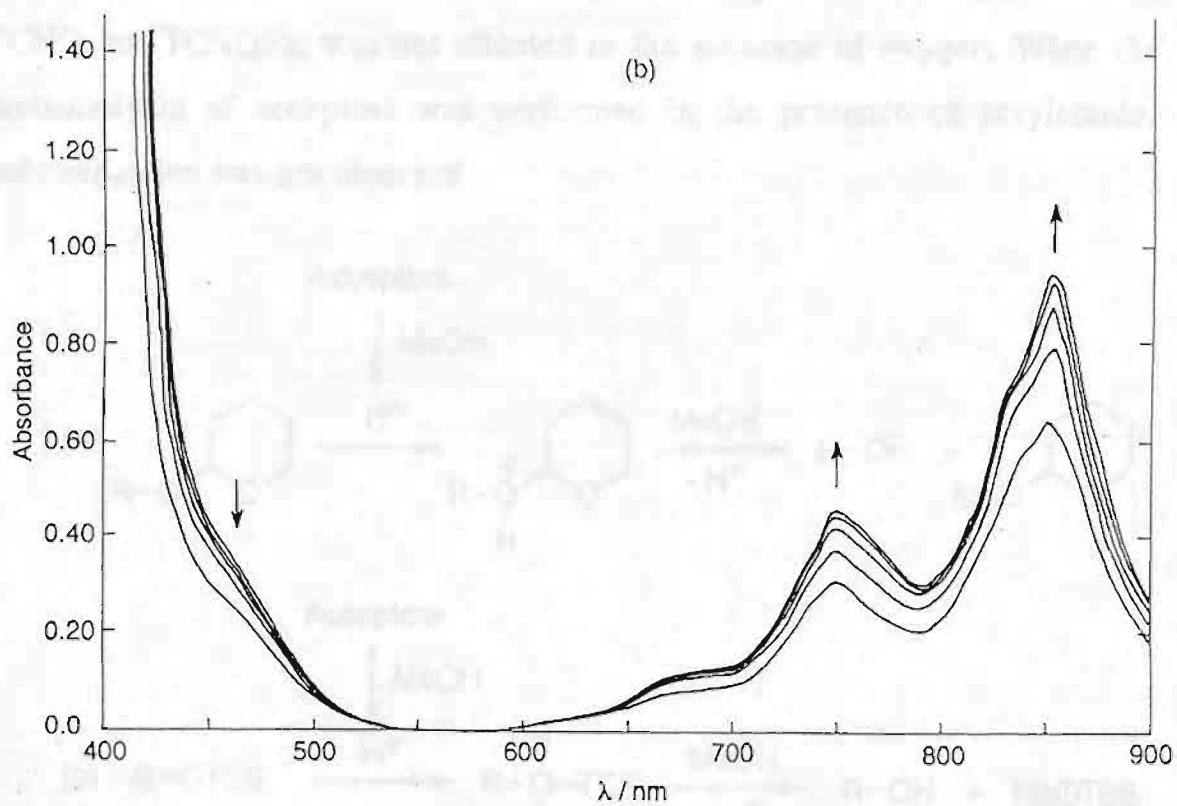
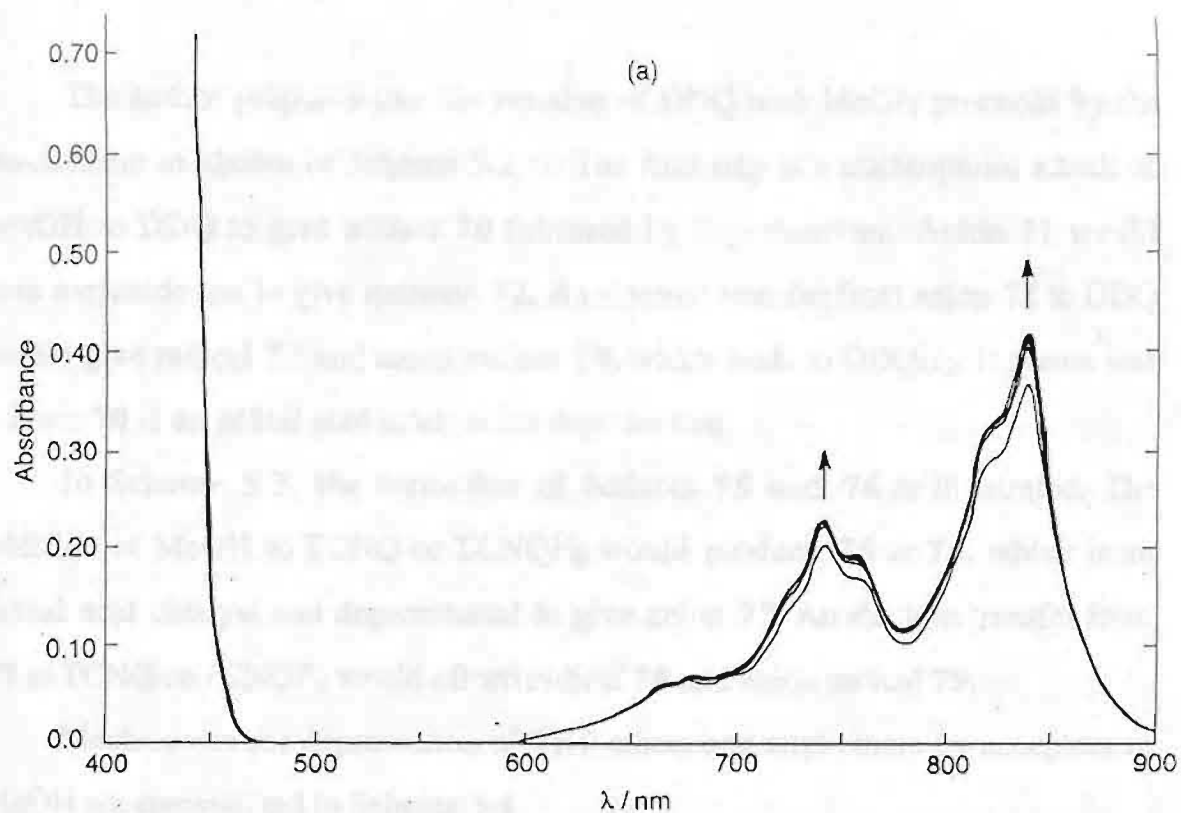


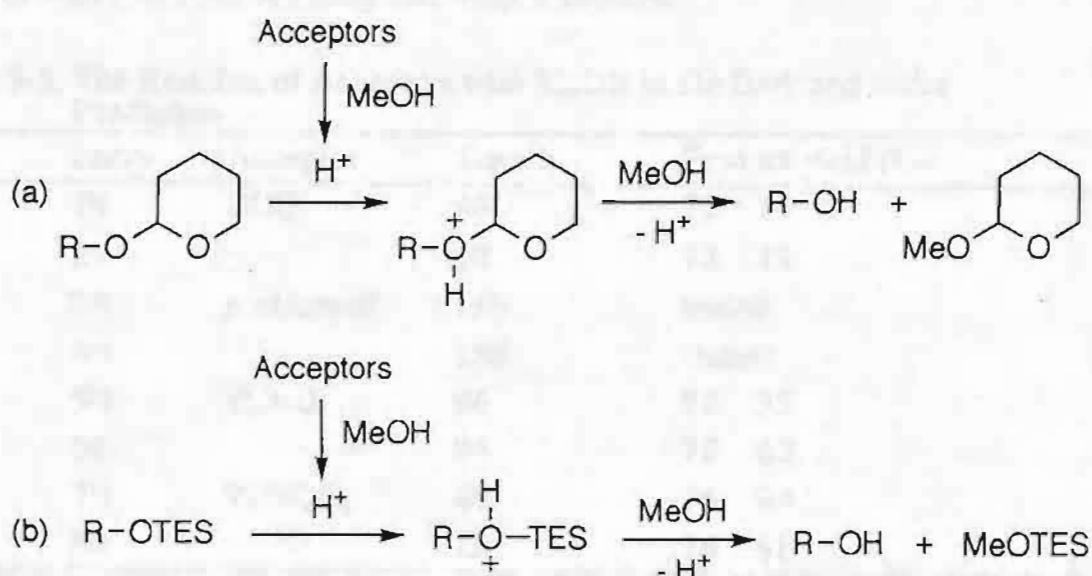
Figure 5-3. (a) Spectral change of TCNQ ( $1.0 \times 10^{-3} \text{ mol dm}^{-3}$ ) in MeOH at room temperature: Curves show spectra at 0, 15, 30, and 45 min (b) Spectral change of TCNQF<sub>4</sub> ( $2.5 \times 10^{-3} \text{ mol dm}^{-3}$ ) in MeOH at room temperature: Curves show spectra at 0, 5, 10, 15, and 20 min

The author proposes that the reaction of DDQ with MeOH proceeds by the mechanism as shown in Scheme 5-2.<sup>19)</sup> The first step is a nucleophilic attack of MeOH to DDQ to give adduct **70** followed by deprotonation. Anion **71** would lose a cyanide ion to give quinone **72**. An electron transfer from anion **71** to DDQ would give radical **73** and anion radical **74**, which leads to DDQH<sub>2</sub>. It seems that adduct **70** is an actual acid catalyst for deprotection.

In Scheme 5-3, the formation of adducts **75** and **76** is illustrated. The addition of MeOH to TCNQ or TCNQF<sub>4</sub> would produce **75** or **76**, which is an actual acid catalyst and deprotonated to give anion **77**. An electron transfer from **77** to TCNQ or TCNQF<sub>4</sub> would afford radical **78** and anion radical **79**.

Mechanisms for deprotection of THP ethers and silyl ethers by acceptors in MeOH are summarized in Scheme 5-4.

Interestingly, the methanolysis of various acceptors, *i.e.*, DDQ, *p*-chloranil, TCNQ, and TCNQF<sub>4</sub>, was not affected in the presence of oxygen. When the methanolysis of acceptors was performed in the presence of acrylamide, polymerization was not observed.



Scheme 5-4.



Formation of the anion radical was also observed in the reactions of MeONa and DDQ, TCNQ, and TCNQF<sub>4</sub>. When MeONa and 2 equiv. of these acceptors were dissolved in MeCN, the stable solution was obtained, which exhibited the absorptions of the corresponding anion radical of the acceptors in the UV-VIS spectra [DDQ anion radical:<sup>20)</sup>  $\lambda_{\text{max}} = 347, 435, 455, 540, \text{ and } 585 \text{ nm}$ ].

Interestingly, the rate of the methanolysis of acceptors was sharply increased by the irradiation of a fluorescent lamp (Table 5-5). In the case of *p*-chloranil, acidic materials could not be isolated from the irradiated solution. However, 1-dodecanol (**48e**) was obtained in 99% yield when THP ether **48a** was treated with the irradiated solution for 7 h, while no reaction occurred when **48a** was treated with the unirradiated solution. By analogy with TCNQ-mesitylene systems,<sup>21)</sup> the adduct formation might be explained in terms of the chemical pseudoexcitation concept<sup>22)</sup> proposed by Fukui *et al*, namely, thermal reactions of strong acceptors such as DDQ or TCNQF<sub>4</sub> with electron-donating substrates resemble photochemical ones of weak acceptors such as *p*-chloranil or TCNQ. In these cases, the rate of reactions were accelerated by the irradiation of a fluorescent lamp in both reactions of strong and weak acceptors.

Table 5-5. The Reaction of Acceptors with MeOH in the Dark and under Irradiation

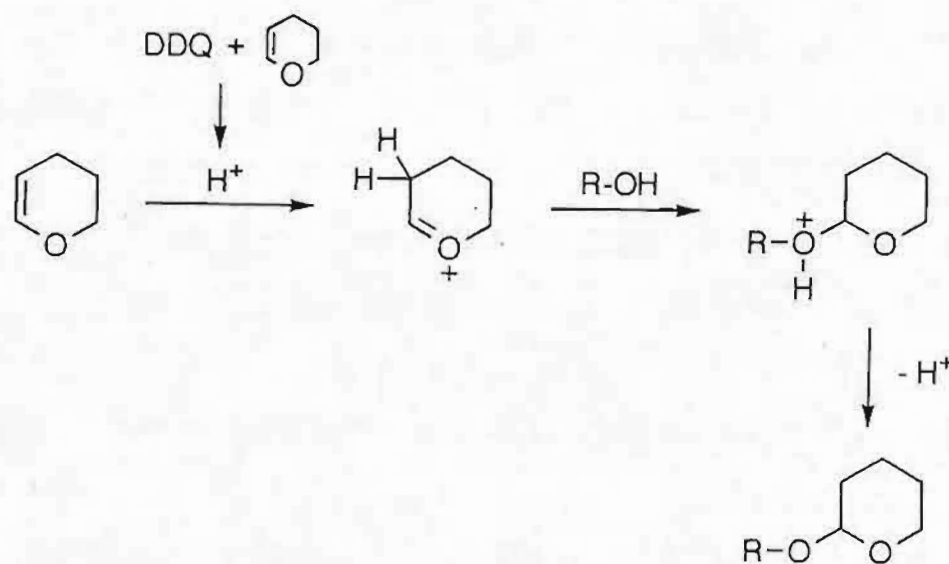
Entry	Acceptor	Time/h	Product yield /% <sup>a)</sup>
1b)	DDQ	48	<b>72</b> 14
2c)		10	<b>72</b> 13
3b)	<i>p</i> -chloranil	158	trace <sup>d)</sup>
4c)		158	trace <sup>e)</sup>
5b)	TCNQ	96	<b>75</b> 33
6c)		96	<b>75</b> 62
7b)	TCNQF <sub>4</sub>	48	<b>76</b> 94
8c)		13	<b>76</b> 91

a) Isolated yields. b) In the dark. c) Irradiated by a fluorescent lamp. d) No reaction was observed when **48a** was treated with the unirradiated solution for 7 h. e) Alcohol **48e** (99%) was obtained from the reaction of **48a** with the irradiated solution for 7 h.



In the cases of the deprotection in aqueous solvents, acceptors such as DDQ, *p*-chloranil, TCNQ, and TCNQF<sub>4</sub>, were decomposed to give unidentified acidic materials. These materials caused the deprotection more rapidly than the corresponding acceptors, indicating that cleavage of the protecting groups was catalyzed by protons generated in the solvents.

For the tetrahydropyranylation of alcohols catalyzed by DDQ, the author conducted a brief examination of the mechanism. DDQH<sub>2</sub> (8 days, 26%) was isolated from the reaction of DHP with DDQ in CH<sub>2</sub>Cl<sub>2</sub>. The above reaction mixture possessed an activity and DDQH<sub>2</sub> did not cause the reactions. From these results, a small amount of unidentified acidic materials would be formed during the reactions. The mechanism of tetrahydropyranylation is summarized in Scheme 5-5.



Scheme 5-5.

## Conclusions

In the presence of a catalytic amount of DDQ, THP ethers **48a-54a** were converted into the corresponding alcohols **48e-54e** in MeOH. The deprotection of TES ethers **48b**, **50b**, **51b**, and **54b**, TBDMS ethers **48c**, **50c**, **51c**, and **54c** and TBDPS ethers **48d**, **50d**, **51d**, and **54d** catalyzed by DDQ was examined in MeOH. TES ethers were cleaved more easily than TBDMS ethers. The deprotection of TBDPS ethers proceeded most slowly among the examined silyl ethers. Strong  $\pi$ -acceptors possessing higher reduction potentials cleaved dodecyl TES ether **48b** much easily. The cleavage of these protecting groups is caused by protons generated from the methanolysis of  $\pi$ -acceptors. The author isolated some active products for deprotection from the reactions of acceptors with MeOH.

## Experimental

All melting points are uncorrected. Column chromatography was performed on Wakogel C-200. IR spectra were recorded on a Hitachi Model 270-30 spectrophotometer.  $^1\text{H}$  (200 MHz, 60 MHz) and  $^{13}\text{C}$  NMR (50 MHz) spectra were measured on a Varian Gemini 200 or a Hitachi R-24B spectrometer using  $\text{Me}_4\text{Si}$  as an internal standard. UV-VIS spectra were recorded on a Hitachi Model 320 spectrophotometer. THP ethers **48a-54a** and silyl ethers **48b-54b**, **48c**, **50c**, **51c**, **54c**, **48d**, **50d**, **51d**, and **54d** were prepared by the reported methods.<sup>23,24</sup> All products obtained in this study were completely characterized by comparison with authentic samples. MeOH was refluxed for 6 h with magnesium methoxide, distilled and stored under nitrogen.  $\pi$ -Acceptors were purified by sublimation or recrystallization from the appropriate solvents.<sup>3</sup> All reactions were carried out under nitrogen in the dark. Acid concentration in MeOH was measured with a pH meter (HORIBA pH Meter M-8E), which was corrected using a scale based on the solution of hydrogen chloride in MeOH. The concentration of the solution of hydrogen chloride in MeOH was determined by titration using the standard solution of sodium carbonate.

Typical Procedure for Deprotection of THP Ethers **48a-54a** Catalyzed by DDQ.

To a solution of dodecyl THP ether **48a** (270 mg, 1.0 mmol) in dry MeOH (8.0 ml) was added a solution of DDQ (23 mg, 0.1 mmol) in dry MeOH (2.0 ml). After the mixture was stirred at room temperature for 7 h, sodium hydrogencarbonate (42 mg, 0.5 mmol) was added. The mixture was evaporated and the residue was chromatographed (hexane-acetone = 5 : 1) on silica gel to give 1-dodecanol **48e** (158 mg, 85%).



#### **48b-d** Catalyzed by DDQ.

To a solution of dodecyl TES ether **48b** (300 mg, 1.0 mmol) in dry MeOH (8.0 ml) was added a solution of DDQ (23 mg, 0.1 mmol) in dry MeOH (2.0 ml). After stirring at room temperature for 30 min, the mixture was worked up as described above to give 1-dodecanol **48e** (167 mg, 90%).

#### Typical Procedure for Deprotection of TES Ethers **48b-54b** Catalyzed by *p*-Chloranil.

A mixture of dodecyl TES ether **48b** (300 mg, 1.0 mmol) and *p*-chloranil (12 mg, 0.05 mmol) in dry MeOH (10.0 ml) was stirred at room temperature for 3 h. The mixture was worked up as described above to give 1-dodecanol **48e** (177 mg, 95%).

#### Typical Procedure for Deprotection of Dodecyl TES Ether **48b** Catalyzed by Various Acceptors.

A mixture of dodecyl TES ether **48b** (300 mg, 1.0 mmol) and TCNQF<sub>4</sub> (28 mg, 0.1 mmol) in dry MeOH (10.0 ml) was stirred at room temperature for 30 min. The mixture was worked up as described above to give 1-dodecanol **48e** (155 mg, 84%).

#### Typical Procedure for the Reactions of $\pi$ -Acceptors in MeOH.

A solution of DDQ (227 mg, 1.0 mmol) in dry MeOH (100.0 ml) was stirred at room temperature for 48 h. After evaporation of the solvent, the mixture of 2,3-dichloro-5-cyano-6-methoxy-*p*-benzoquinone (**72**) (12%) and DDQH<sub>2</sub> (22%) was obtained together with a large amount of DDQ. The yields were determined by <sup>1</sup>H NMR spectroscopy.

DDQH<sub>2</sub> was isolated by the following procedure: The above reaction mixture was dissolved in ether (25.0 ml). The ethereal solution was extracted with

saturated sodium hydrogencarbonate solution (50.0 ml). The alkaline solution was acidified with 6 M-hydrochloric acid and the resulting mixture was extracted with ether twice. The extracts were washed, dried and evaporated to give DDQH<sub>2</sub> (46 mg, 20%).

Quinone **72** was isolated by the following procedure: A solution of DDQ (2.27 g, 10 mmol) in dry MeOH (10 ml) was kept standing at room temperature for 48 h. The resulting precipitate was removed by filtration to give **72** (324 mg, 14%), yellow plates, mp 222-223 °C (from acetone) (*lit.*,<sup>16</sup> 225-226 °C); IR (KBr) 2968, 2232, 1698, 1680, 1666, 1620, 1582, 1336, 1286, 1238, 1170, 1102, 978, 882, 804, 732, 720, and 608 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>, 60 MHz) 4.52 (3H, s, MeO).

*α*-Methoxy-*p*-phenylenedimalononitrile (**75**).

Colorless crystals, mp > 250 °C (from acetone-hexane); IR (KBr) 3052, 2888, 2192, 1580, 1508, 1414, 1180, 1092, 1048, 988, 852, and 784 cm<sup>-1</sup>; UV (MeOH) 224 (ε 15000 dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>), 270 (19800), and 335 nm (21000); <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>, 60 MHz) 3.84 (3H, s, MeO), 6.27 (1H, br s, CH(CN)<sub>2</sub>), and 7.99 (4H, s, ArH). CH proton was exchanged with D<sub>2</sub>O. Found: C, 66.31; H, 3.34%. Calcd for C<sub>13</sub>H<sub>8</sub>N<sub>4</sub>O: C, 66.10; H, 3.41%.

*α*-Methoxy-2,3,5,6-tetrafluoro-*p*-phenylenedimalononitrile (**76**).

Colorless crystals, mp 131-134 °C (dec) (from acetone-hexane); IR (KBr) 2928, 2196, 2160, 1498, 1480, 1322, 1286, 1074, 1068, 974, 952, and 764 cm<sup>-1</sup>; UV (MeOH) 216 (ε 18100 dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>), 265 (7000), and 332 nm (32000); <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>, 60 MHz) 3.81 (3H, s, MeO) and 6.55 (1H, br s, CH(CN)<sub>2</sub>). CH proton was exchanged with D<sub>2</sub>O; <sup>13</sup>C NMR (CD<sub>3</sub>COCD<sub>3</sub>, 50 MHz) 18.5 (d), 57.2 (q), 65.2 (s), 110.7 (s), 111.2 (s), 143.0 (s), 143.4 (s), 148.1 (s), and 148.4 (s). Found: C, 50.62; H, 1.40%. Calcd for C<sub>13</sub>H<sub>4</sub>N<sub>4</sub>OF<sub>4</sub>: C, 50.66; H, 1.31%.

Quenching Experiments.

To a solution of dodecyl THP ether **48a** (270 mg, 1.0 mmol) in dry MeOH (5.0 ml) was added a mixture of compound **76** (31 mg, 0.1 mmol) and DTBP (76 mg, 0.4 mmol) in dry MeOH (5.0 ml). After stirring at room temperature for 30 min, the mixture was worked up as described above and the starting material **48a** (266 mg, 99%) was recovered.

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## Chapter 6. Oxidative Removal of 1,3-Dithiane Protecting Groups by DDQ

Deprotection of dithioacetals to the corresponding carbonyl compounds is one of the most important reactions in synthetic organic chemistry.<sup>1)</sup> For this transformation, many procedures such as mercury (II) salts-induced, alkylative, halogenative, and oxidative<sup>2,3)</sup> hydrolyses are known. However, it is necessary to develop a mild and efficient method because mercury salts are highly toxic and some oxidative methods require drastic conditions or inconvenient procedures. In this chapter, the reactions of dithioacetals **80-82** with DDQ in aqueous MeCN are described.

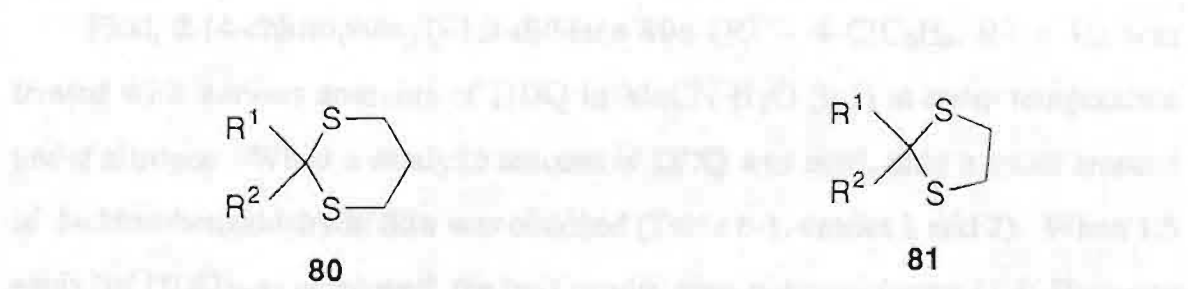


Table 6-1. The effect of various substituents on the polymerization of 1,2-ethanedithiol with 1,2-ethanedithiol.

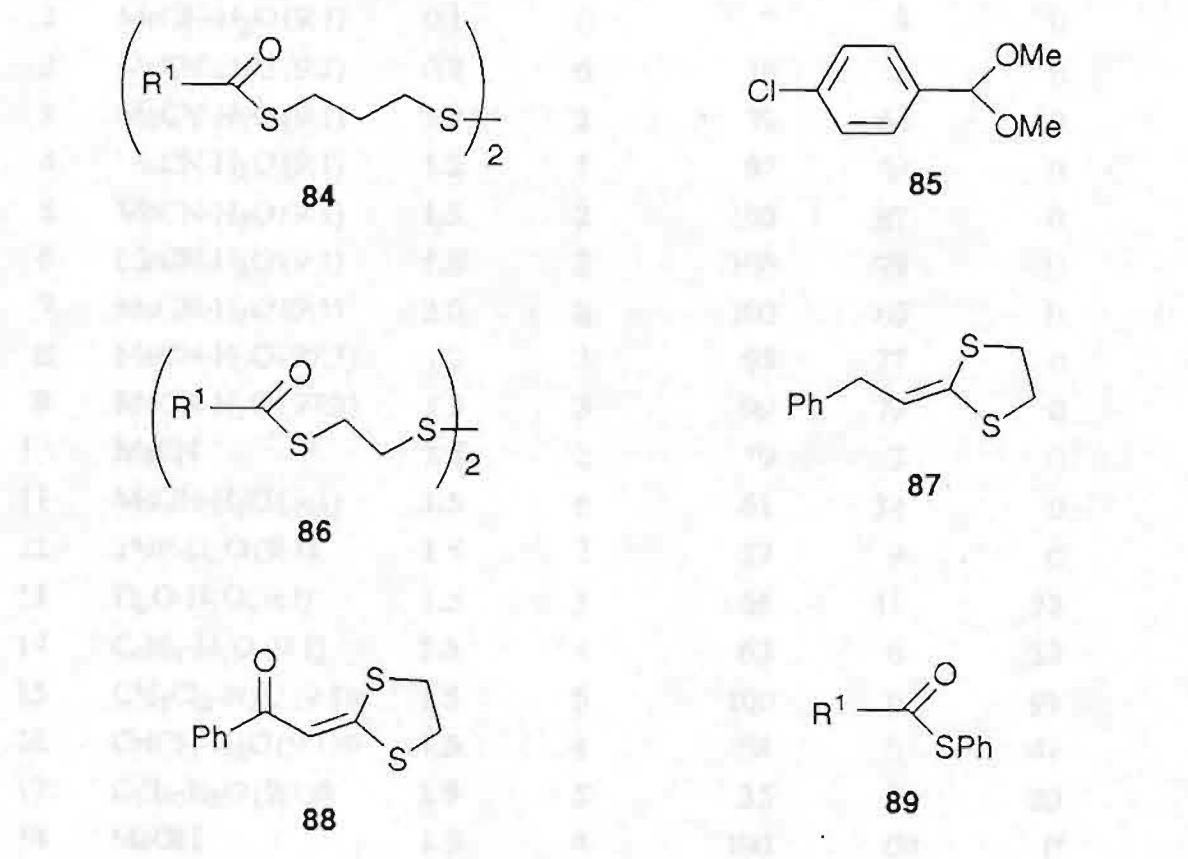


Figure 6-1.

First, 2-(4-chlorophenyl)-1,3-dithiane **80a** ( $R^1 = 4\text{-ClC}_6\text{H}_4$ ,  $R^2 = \text{H}$ ) was treated with various amounts of DDQ in MeCN-H<sub>2</sub>O (9:1) at room temperature under nitrogen. When a catalytic amount of DDQ was used, only a small amount of 4-chlorobenzaldehyde **83a** was obtained (Table 6-1, entries 1 and 2). When 1.5 equiv. of DDQ was employed, the best results were obtained (entry 5).<sup>4)</sup> Decrease of the water ratio (MeCN:H<sub>2</sub>O = 97:3) somewhat lowered the yields (entries 8 and 9). In the absence of water, most of dithiane **80a** was recovered (entry 10).

Table 6-1. The Reaction of Dithiane **80a** with DDQ in Various Solvents<sup>a)</sup>

Entry	Solvent	DDQ / mmol	Time / h	Conv. / %	Yield / % <sup>b)</sup>	
					<b>83a</b>	<b>84a</b>
1	MeCN-H <sub>2</sub> O (9:1)	0.1	6	7	3	0
2	MeCN-H <sub>2</sub> O (9:1)	0.2	6	16	8	0
3	MeCN-H <sub>2</sub> O (9:1)	1.0	3	79	64	0
4	MeCN-H <sub>2</sub> O (9:1)	1.2	3	87	69	0
5	MeCN-H <sub>2</sub> O (9:1)	1.5	2	100	87	0
6	MeCN-H <sub>2</sub> O (9:1)	1.8	2	100	79	0
7	MeCN-H <sub>2</sub> O (9:1)	2.0	2	100	60	0
8	MeCN-H <sub>2</sub> O (97:3)	1.2	3	95	77	0
9	MeCN-H <sub>2</sub> O (97:3)	1.5	3	99	77	0
10	MeCN	1.5	2	19	7	0
11	MeOH-H <sub>2</sub> O (9:1)	1.5	6	61	32	0
12	THF-H <sub>2</sub> O (9:1)	1.5	2	27	9	0
13	Et <sub>2</sub> O-H <sub>2</sub> O (9:1)	1.5	3	56	31	22
14	C <sub>6</sub> H <sub>6</sub> -H <sub>2</sub> O (9:1)	1.5	4	62	0	39
15	CH <sub>2</sub> Cl <sub>2</sub> -H <sub>2</sub> O (9:1) <sup>c)</sup>	1.5	5	100	0	93
16	CHCl <sub>3</sub> -H <sub>2</sub> O (9:1) <sup>d)</sup>	1.5	4	53	0	47
17	CCl <sub>4</sub> -H <sub>2</sub> O (9:1) <sup>d)</sup>	1.5	5	35	0	20
18	MeOH	1.5	4	100	0 <sup>e)</sup>	0

a) DDQ in solvent (1.5 ml) was added to a solution of dithiane **80a** (1.0 mmol) in solvent (5.5 ml) at room temperature under nitrogen. b) Isolated yields. c) 14 ml of the solvent was used. d) 10 ml of the solvent was used. e) Acetal **85** was obtained in 82% yield.



Solvent effect on product yields was examined using 1.5 equiv. of DDQ. In polar solvents such as MeCN-H<sub>2</sub>O (9:1) or MeOH-H<sub>2</sub>O (9:1), dithiane **80a** was hydrolyzed to give aldehyde **83a** (entries 5 and 11). In less polar solvents such as C<sub>6</sub>H<sub>6</sub>-H<sub>2</sub>O (9:1) or CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O (9:1), thioester **84a** (R<sup>1</sup> = 4-ClC<sub>6</sub>H<sub>4</sub>) was produced exclusively (entries 14 and 15). In MeOH, an exchange reaction was observed, leading to dimethyl acetal **85** (entry 18).<sup>5</sup>

Hydrolysis of various dithianes **80** was examined in MeCN-H<sub>2</sub>O (9:1). The results are summarized in Table 6-2. In most cases, the reaction proceeds smoothly to give the corresponding aldehydes or ketones in good yields. Dithianes **80b** and **80c** possessing an electron-withdrawing group such as nitro and cyano groups on the benzene ring require longer reaction time (entries 1 and 2). Dithianes **80g-i** bearing electron-donative groups on the benzene ring afforded thioesters **84g-i** together with aldehydes **83g-i** (entries 7-9). Recently, Sankararaman *et al.*<sup>6</sup> have reported the photochemical and thermal (reflux conditions) methods for deprotection of dithioacetals using DDQ in MeCN. Although they explained that the mixtures of dithioacetals and DDQ were stable in MeCN at room temperature when protected from room light, deprotection of 1,3-dithianes proceeded at the almost same rate even in the dark under the aqueous conditions.

Table 6-2. The Reaction of Dithianes **80** with DDQ in MeCN-H<sub>2</sub>O (9:1)

Entry	Substrate	R <sup>1</sup>	R <sup>2</sup>	Time / h	Conv. / %	Yield / % <sup>a)</sup>	
						<b>83</b>	<b>84</b>
1	<b>80b</b>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	6	66	30	0
2	<b>80c</b>	4-NCC <sub>6</sub> H <sub>4</sub>	H	6	76	61	0
3	<b>80d</b>	4-MeOCOC <sub>6</sub> H <sub>4</sub>	H	3	100	97	0
4	<b>80a</b>	4-ClC <sub>6</sub> H <sub>4</sub>	H	2	100	87	0
5	<b>80e</b>	4-PhC <sub>6</sub> H <sub>4</sub>	H	2	100	92	0
6	<b>80f</b>	Ph	H	1	100	70 <sup>b)</sup>	0
7	<b>80g</b>	4-MeC <sub>6</sub> H <sub>4</sub>	H	3	100	88	8
8	<b>80h</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	H	2	100	43	41
9	<b>80i</b>	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	1	100	23	74
10	<b>80j</b>	PhCH <sub>2</sub> CH <sub>2</sub>	H	2	91	70	0
11	<b>80k</b>	<i>n</i> -C <sub>11</sub> H <sub>23</sub>	H	1	95	71	0
12	<b>80l</b>	Ph	Me	0.5	100	75	-
13	<b>80m</b>	Ph	Ph	2	87	82	-
14	<b>80n</b>	-(CH <sub>2</sub> ) <sub>2</sub> CH( <i>t</i> -Bu)(CH <sub>2</sub> ) <sub>2</sub> -		1.5	97	81	-
15	<b>80o</b>	<i>n</i> -C <sub>9</sub> H <sub>19</sub>	Me	1	100	87	-

a) Isolated yields. b) Determined by <sup>1</sup>H NMR spectroscopy.

Next, the reactions of 1,3-dithiolanes **81** with DDQ were examined. The results are summarized in Table 6-3. In these cases, conversion of 1,3-dithiolanes **81** to the corresponding carbonyl compounds was much slower than that of dithianes **80**. In the cases of 1,3-dithiolanes **81** derived from aromatic aldehydes, thioesters **86** were obtained as major products (entries 1-3). 2-(2-Phenylethyl)-1,3-dithiolane **81j** reacted with DDQ to give **87** (3%) and **88** (20%) in addition to a small amount of the deprotected **83j** (7%) (entry 4). In the case of **81k**, the reaction occurred, however, many unidentified products were obtained together with a small amount of the parent aldehyde **83k** (21%) (entry 5). 1,3-Dithiolanes **81** derived from aliphatic and aromatic ketones were stable under these reaction conditions (entries 6-9).



Table 6-3. The Reaction of Dithiolanes **81** with DDQ in MeCN-H<sub>2</sub>O (9:1)

Entry	Substrate	R <sup>1</sup>	R <sup>2</sup>	Time / h	Conv. / %	Yield / % <sup>a)</sup>	
						<b>83</b>	<b>86</b>
1	<b>81a</b>	4-ClC <sub>6</sub> H <sub>4</sub>	H	0.5	84	11	70
2	<b>81g</b>	4-MeC <sub>6</sub> H <sub>4</sub>	H	1	100	2	75
3	<b>81h</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	H	1	100	15	69
4	<b>81j</b>	PhCH <sub>2</sub> CH <sub>2</sub>	H	1	62	7	0 <sup>b)</sup>
5	<b>81k</b>	<i>n</i> -C <sub>11</sub> H <sub>23</sub>	H	1	58	21	0
6	<b>81l</b>	Ph	Me	2	21	2	-
7	<b>81m</b>	Ph	Ph	2	19	1	-
8	<b>81n</b>	-(CH <sub>2</sub> ) <sub>2</sub> CH( <i>t</i> -Bu)(CH <sub>2</sub> ) <sub>2</sub> -		1	14	1	-
9	<b>81o</b>	<i>n</i> -C <sub>9</sub> H <sub>19</sub>	Me	2	12	6	-

a) Isolated yields. b) Compounds **87** and **88** were obtained in 3 and 20% yields, respectively.

Most of *S,S'*-diphenyl dithioacetals **82** were inert under the conditions employed (Table 6-4). Only compounds **82h** and **82i** possessing electron-donative substituents on the benzene ring were converted to the corresponding aldehydes **83h** and **83i** in good yields, respectively (entries 2 and 3). In these cases, a large amount of diphenyl disulfide was isolated. Thioesters **89** were not detected by TLC or <sup>1</sup>H NMR spectroscopy.

Table 6-4. The Reaction of Diphenyl Dithioacetals **82** with DDQ in MeCN-H<sub>2</sub>O (9:1)

Entry	Substrate	R <sup>1</sup>	R <sup>2</sup>	Time / h	Conv. / %	Yield <sup>a)</sup> of <b>83</b> / %
1	<b>82a</b>	4-ClC <sub>6</sub> H <sub>4</sub>	H	3	16	0
2	<b>82h</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	H	1	100	78
3	<b>82i</b>	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	1	100	78
4	<b>82j</b>	PhCH <sub>2</sub> CH <sub>2</sub>	H	5	20	0
5	<b>82k</b>	<i>n</i> -C <sub>11</sub> H <sub>23</sub>	H	5	20	0
6	<b>82l</b>	Ph	Me	5	18	0
7	<b>82n</b>	-(CH <sub>2</sub> ) <sub>2</sub> CH( <i>t</i> -Bu)(CH <sub>2</sub> ) <sub>2</sub> -		5	13	0
8	<b>82o</b>	<i>n</i> -C <sub>9</sub> H <sub>19</sub>	Me	5	26	0

a) Isolated yields.



Taking account of the difference in reactivity of these dithioacetals **80-82**, the competitive cleavage reactions of 1,3-dithiane **80** in the presence of 1,3-dithiolane **81** or *S,S'*-diphenyl dithioacetal **82** was investigated. Indeed, the treatment of dithianes **80** with 1.2 equiv. of DDQ in MeCN-H<sub>2</sub>O (97:3) in the presence of dithiolanes **81** or *S,S'*-diphenyl dithioacetals **82** caused hydrolysis of **80** without appreciable changes of **81** or **82** (Table 6-5). In fact, the mixture of **80a** and **81a**, dithiane **80a** was effectively transformed to aldehyde **83a** without conversion of **81a** to thioester **86a** (entry 5).

Table 6-5. Competitive Cleavage Reaction of Dithianes **80** in the Presence of Dithiolanes **81** or Diphenyl Dithioacetals **82** with DDQ in MeCN-H<sub>2</sub>O (9:1)

Entry	R <sup>1</sup>	R <sup>2</sup>	Compounds	Time / h	Products (Yield/% <sup>a</sup> )
1	-(CH <sub>2</sub> ) <sub>2</sub> CH(t-Bu)(CH <sub>2</sub> ) <sub>2</sub> -		<b>80n+81n</b>	3	<b>80n</b> (11%) <b>81n</b> (97%) <b>83n</b> (86%)
2			<b>80n+82n</b>	3	<b>80n</b> ( 8%) <b>82n</b> (95%) <b>83n</b> (86%)
3	n-C <sub>9</sub> H <sub>19</sub>	Me	<b>80o+81o</b>	2	<b>80o</b> (10%) <b>81o</b> (95%) <b>83o</b> (89%)
4			<b>80o+82o</b>	2	<b>80o</b> (10%) <b>82o</b> (91%) <b>83o</b> (90%)
5	4-ClC <sub>6</sub> H <sub>4</sub>	H	<b>80a+81a</b>	3	<b>80a</b> (12%) <b>81a</b> (90%) <b>83a</b> (80%)
6			<b>80a+82a</b>	3	<b>80a</b> (10%) <b>82a</b> (93%) <b>83a</b> (83%)

a) Isolated yields.

As shown in Scheme 6-1, the formation of aldehyde **83** and thioester **84** would be explained by the SET mechanism although the precise one is not clear at this moment.<sup>7)</sup> The first step is a SET process from dithiane **80** to DDQ via a charge-transfer (CT) complex to give a geminate radical ion pair. The resulting cation radical **90** is stabilized by a transannular interaction with the adjacent sulfur atom.<sup>8)</sup> Subsequent reactions of the radical ion pair, which involve diffusion to cation radical **91** and DDQ anion radical, the attack by water and the second SET process, would lead to aldehyde **83**.

Scheme 6-1.



The reaction pathways would be supported by the following facts. During the reaction, a dark red colouration due to the formation of CT complex was observed. CT absorption maxima were 544 and 584 nm for **80a**. 1,2-Dithiolane **94** (2%),<sup>9)</sup> polymeric organosulfur compound **95** (42%)<sup>9)</sup> and DDQH<sub>2</sub> (1.0 equiv.) were isolated from the reaction of **80a** with DDQ. 1,2-Dithiolane **94** was unstable at ambient temperature and underwent a facile polymerization to the polymeric **95**. Addition of 1,2,4,5-tetramethoxybenzene (TMB) (1.5 equiv.) to **80I**, which is a SET quencher, suppressed the formation of **83I** (2%), while 1,4-dimethoxybenzene (DMB) did not affect the results at all [ $E_{\text{ox}}$  (**80I**) = 1.13 V,<sup>7a)</sup>  $E_{\text{ox}}$  (TMB) = 0.77 V,<sup>2c)</sup>  $E_{\text{ox}}$  (DMB) = 1.28 V<sup>2c)</sup> (vs. SCE in MeCN)]. These results suggest that SET processes are involved in the reaction. An acid-catalysed mechanism was ruled out since acidic materials<sup>10)</sup> generated from complete decomposition of DDQ in aqueous MeCN did not cause deprotection of **80a** at all. Interestingly, the yield of **83** was not reduced at all in the presence of oxygen, which was in contrast to the other SET reactions of dithioacetals.<sup>2b,7b)</sup>

On the other hand, proton transfer from cation radical **90** to DDQ anion radical followed by the second SET process would lead to a geminate ion pair.<sup>11)</sup> Cation **97** is hydrolyzed to give thiol **98**, which is further oxidized to **84** by DDQ. Under these reaction conditions employed, thiols such as 1-dodecanethiol were oxidized to disulfides rapidly by DDQ. Oxidation of *p*-methoxybenzylidene acetals to the corresponding esters by DDQ is known and explained by the similar mechanism.<sup>12)</sup>

In polar solvents such as aqueous MeCN, which encourage the radical ion pair to escape from the solvent cage, deprotection occurred predominantly.<sup>13)</sup> In less polar solvents, proton transfer within the solvent cage is favored to lead to thioester **84**. The effect of substituents on the benzene ring is consistent with the proposed mechanism. For dithianes bearing electron-withdrawing groups on the benzene ring, longer reaction time was required because the first SET process

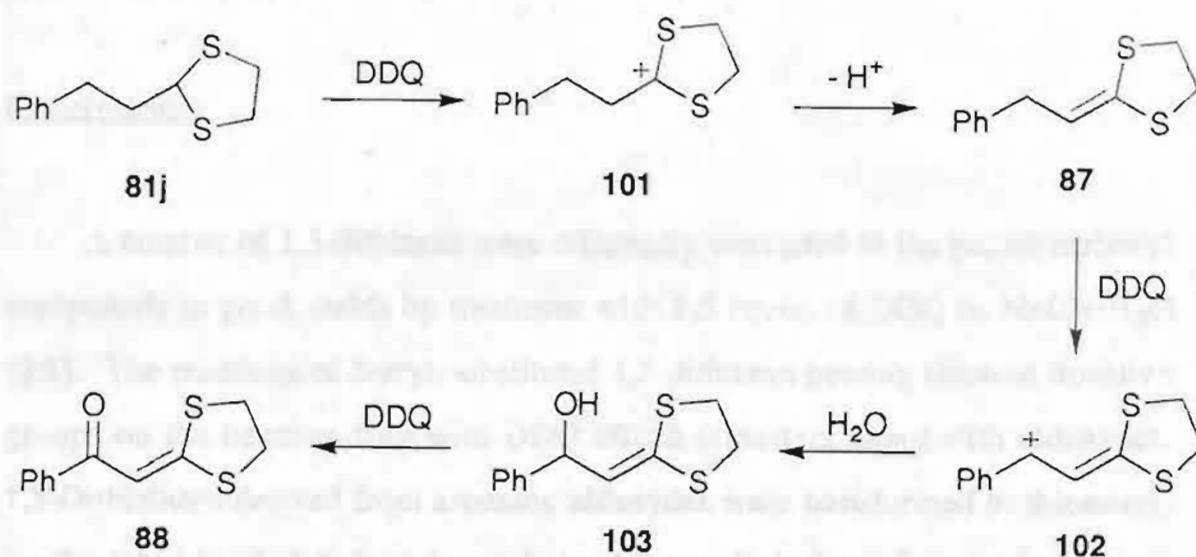


proceeds with much more difficulty and deprotection proceeded exclusively since benzylic cation **97** is destabilized. In contrast, electron-donative groups markedly promote the formation of thioester **84**.

In the case of dithiolane **81**, cation radical **99** is less stable than dithiane cation radical **90** because of the absence of a transannular interaction,<sup>8)</sup> therefore, **99** is transformed to thioester **86** or returns to the starting **81** before escape from the solvent cage. From the reaction of compound **81j** with DDQ, compounds **87** and **88** were obtained. The mechanism is shown in Scheme 6-2. Hydride transfer from dithiolane **81j** to DDQ affords cation **101**, which is deprotonated to give compound **87**. Product **88** would be produced by benzylic oxidation of **87** with DDQ followed by the addition of water and DDQ oxidation.

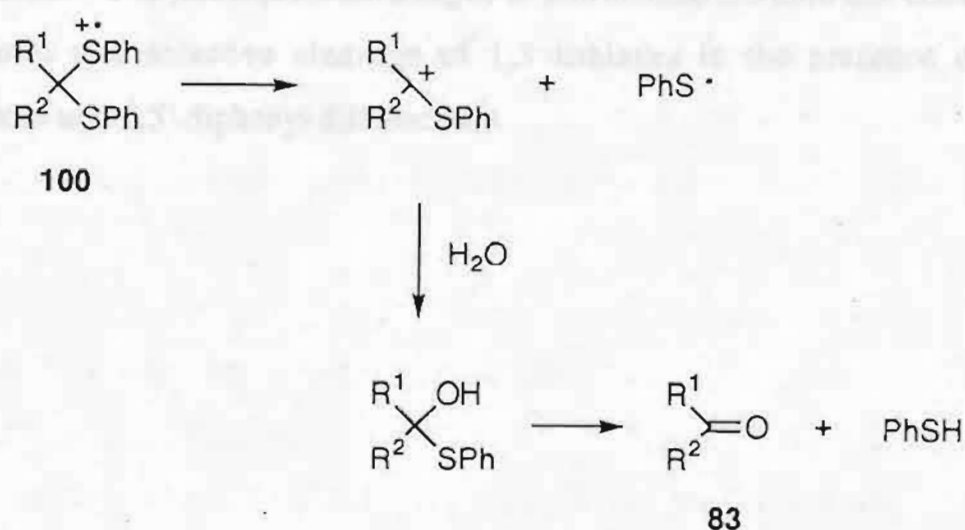


Figure 6-2.



Scheme 6-2.

In contrast, cation radical 100 generated from *S,S'*-diphenyl dithioacetal 82 would be cleaved to carbocation and stable phenylthio radical. The resulting cation is hydrolyzed to give carbonyl compound 83 (Scheme 6-3).



Scheme 6-3.

## Conclusions

A number of 1,3-dithianes were efficiently converted to the parent carbonyl compounds in good yields by treatment with 1.5 equiv. of DDQ in MeCN-H<sub>2</sub>O (9:1). The reactions of 2-aryl-substituted 1,3-dithianes bearing electron-donative groups on the benzene ring with DDQ afford thioesters along with aldehydes. 1,3-Dithiolanes derived from aromatic aldehydes were transformed to thioesters, on the other hand, 1,3-dithiolanes derived from aliphatic and aromatic ketones were stable under these reaction conditions. *S,S'*-Diphenyl dithioacetals were stable except for 4-methoxy- and 3,4-dimethoxybenzaldehyde *S,S'*-diphenyl dithioacetals which give the corresponding aldehydes. Selective cleavage reactions of 1,3-dithiane in the presence of 1,3-dithiolane or *S,S'*-diphenyl dithioacetal were performed.

The present method constitutes a useful methodology for deprotection of 1,3-dithianes. The remarkable advantages of this method are mild and convenient procedures and selective cleavage of 1,3-dithianes in the presence of 1,3-dithiolanes and *S,S'*-diphenyl dithioacetals.



## Experimental

All melting points are uncorrected. Column chromatography was performed on Wakogel C-200. DDQ was recrystallized from benzene-hexane. IR spectra were recorded on a Hitachi Model 270-30 spectrophotometer.  $^1\text{H}$  (90 MHz) and  $^{13}\text{C}$  NMR (22.49 MHz) spectra were measured on a JEOL JNM-FX 90Q spectrometer using  $\text{Me}_4\text{Si}$  as an internal standard. UV spectra were recorded on a Hitachi Model 320 spectrophotometer. Dithioacetals **80-82** were prepared by the reported methods.<sup>14,15)</sup>

General Procedure for the Reaction of Dithioacetals **80-82** with DDQ in  $\text{MeCN-H}_2\text{O}$  (9:1).

To a solution of dithiane **80a** (231 mg, 1.0 mmol) in  $\text{MeCN}$  (4.8 ml) and  $\text{H}_2\text{O}$  (0.7 ml), was added a solution of DDQ (341 mg, 1.5 mmol) in  $\text{MeCN}$  (1.5 ml) under nitrogen. After stirring at room temperature for 2 h, the mixture was quenched with saturated sodium hydrogencarbonate (50 ml) and extracted with ether. The extracts were washed with water, dried and evaporated and the residue was chromatographed (benzene) on silica gel to give 4-chlorobenzaldehyde **83a** (122 mg, 87%).

Bis[3-(4-chlorobenzoylsulfanyl)propyl]disulfide **84a**.

Colorless oil; IR (neat)  $1670\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.12 (4H, tt,  $J = 7.0$  and  $7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 2.80 (4H, t,  $J = 7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 3.18 (4H, t,  $J = 7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 7.38 (4H, d,  $J = 8.3\text{ Hz}$ , ArH), and 7.87 (4H, d,  $J = 8.3\text{ Hz}$ , ArH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 27.7 (t), 29.0 (t), 37.6 (t), 128.5 (d), 128.9 (d), 135.3 (s), 139.7 (s), and 190.1 (s). Found: C, 49.16; H, 4.36%. Calcd for  $\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{O}_2\text{S}_4$ : C, 48.87; H, 4.10%.

Bis[3-(4-methylbenzoylsulfanyl)propyl]disulfide **84g**.

Colorless oil; IR (neat)  $1665\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.11 (4H, tt,  $J = 7.0$  and  $7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 2.40 (6H, s, Me), 2.80 (4H, t,  $J = 7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 3.16 (4H, t,  $J = 7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 7.22 (4H, d,  $J = 8.4\text{ Hz}$ , ArH), and 7.86 (4H, d,  $J = 8.4\text{ Hz}$ , ArH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 21.4 (q), 28.4 (t), 29.7 (t), 37.9 (t), 127.6 (d), 129.1 (d), 134.7 (s), 143.9 (s), and 190.2 (s). Found: C, 58.83; H, 5.90%. Calcd for  $\text{C}_{22}\text{H}_{26}\text{O}_2\text{S}_4$ : C, 58.63; H, 5.81%.

**Bis[3-(4-methoxybenzoylsulfanyl)propyl]disulfide 84h.**

Colorless oil; IR (neat)  $1660\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.10 (4H, tt,  $J = 7.0$  and  $7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 2.79 (4H, t,  $J = 7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 3.15 (4H, t,  $J = 7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 3.85 (6H, s, MeO), 6.91 (4H, d,  $J = 8.9\text{ Hz}$ , ArH), and 7.93 (4H, d,  $J = 8.9\text{ Hz}$ , ArH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 28.1 (t), 37.4 (t), 37.9 (t), 55.2 (q), 113.5 (d), 129.1 (d), 129.3 (s), 163.6 (s), and 189.0 (s). Found: C, 54.44; H, 5.58%. Calcd for  $\text{C}_{22}\text{H}_{26}\text{O}_4\text{S}_4$ : C, 54.74; H, 5.43%.

**Bis[3-(3,4-dimethoxybenzoylsulfanyl)propyl]disulfide 84i.**

Colorless oil; IR (neat)  $1660\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.03 (4H, tt,  $J = 7.0$  and  $7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 2.80 (4H, t,  $J = 7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 3.17 (4H, t,  $J = 7.0\text{ Hz}$ ,  $\text{CH}_2$ ), 3.93 (12H, s, MeO), 6.87 (2H, d,  $J = 8.5\text{ Hz}$ , ArH), and 7.32-7.71 (4H, m, ArH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 27.5 (t), 29.1 (t), 37.5 (t), 56.0 (q), 56.1 (q), 109.4 (d), 110.2 (d), 121.7 (d), 129.9 (s), 148.9 (s), 153.4 (s), and 190.1 (s). Found: C, 53.01; H, 5.81%. Calcd for  $\text{C}_{24}\text{H}_{30}\text{O}_6\text{S}_4$ : C, 53.11; H, 5.57%.

**Bis[2-(4-chlorobenzoylsulfanyl)ethyl]disulfide 86a.**

Colorless oil; IR (neat)  $1660\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.84-3.10 (4H, m,  $\text{CH}_2$ ), 3.30-3.52 (4H, m,  $\text{CH}_2$ ), 7.41 (4H, d,  $J = 8.5\text{ Hz}$ , ArH), and 7.89 (4H, d,  $J = 8.5\text{ Hz}$ , ArH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 28.6 (t), 37.9 (t), 128.6 (d), 128.9 (d), 135.0 (s), 139.9 (s), and 190.0 (s). Found: C, 46.44; H, 3.41%. Calcd for  $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{O}_2\text{S}_4$ : C, 46.44; H, 3.41%.



46.65; H, 3.48%.

**Bis[2-(4-methylbenzoylsulfanyl)ethyl]disulfide 86g.**

Colorless oil; IR (neat) 1660  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.40 (6H, s, Me), 2.90-3.08 (4H, m,  $\text{CH}_2$ ), 3.35-3.46 (4H, m,  $\text{CH}_2$ ), 7.24 (4H, d,  $J = 8.2$  Hz, ArH), and 7.86 (4H, d,  $J = 8.2$ , ArH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 21.7 (q), 28.4 (t), 38.1 (t), 127.4 (d), 129.3 (d), 134.3 (s), 144.4 (s), and 189.2 (s). Found: C, 56.54; H, 5.54%. Calcd for  $\text{C}_{20}\text{H}_{22}\text{O}_2\text{S}_4$ : C, 56.84; H, 5.25%.

**Bis[2-(4-methoxybenzoylsulfanyl)ethyl]disulfide 86h.**

Colorless oil; IR (neat) 1660  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.86-3.07 (4H, m,  $\text{CH}_2$ ), 3.31-3.50 (4H, m,  $\text{CH}_2$ ), 3.84 (6H, s, MeO), 6.90 (4H, d,  $J = 8.8$  Hz, ArH), and 7.92 (4H, d,  $J = 8.8$  Hz, ArH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 28.1 (t), 37.9 (t), 55.1 (q), 113.9 (d), 129.3 (d), 131.5 (s), 163.5 (s), and 189.0 (s). Found: C, 52.64; H, 4.90%. Calcd for  $\text{C}_{20}\text{H}_{22}\text{O}_4\text{S}_4$ : C, 52.84; H, 4.88%.

**2-(2-Phenylethylidene)-1,3-dithiolane 87.**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.69-3.25 (6H, m,  $\text{CH}_2$ ), and 7.01-7.36 (6H, m, ArH and C=CH). Found: C, 63.71; H, 5.90%. Calcd for  $\text{C}_{11}\text{H}_{12}\text{S}_2$ : C, 63.42; H, 5.81%.

**2-Benzoylmethylidene-1,3-dithiolane 88.**

Pale yellow prisms, mp 79-80  $^\circ\text{C}$  (from benzene-hexane); IR (KBr) 1610  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 3.36-3.49 (4H, m,  $\text{CH}_2$ ), 7.24-7.54 (4H, m, ArH and C=CH), and 7.89-7.99 (2H, m, ArH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 35.4 (t), 38.9 (t), 108.1 (d), 127.7 (d), 128.5 (d), 131.9 (d), 138.3 (s), 168.3 (s), and 185.6 (s). Found: C, 59.52; H, 4.66%. Calcd for  $\text{C}_{11}\text{H}_{10}\text{OS}_2$ : C, 59.43; H, 4.53%.



### Quenching Experiments.

To the mixture of dithiane **80I** (210 mg, 1.0 mmol) and tetramethoxybenzene (297 mg, 1.5 mmol) in MeCN (4.8 ml) and H<sub>2</sub>O (0.7 ml), was added a solution of DDQ (341 mg, 1.5 mmol) in MeCN (1.5 ml) under nitrogen. After stirring at room temperature for 0.5 h, the mixture was worked up as described above to give dithiane **80I** (191 mg, 91%) and aldehyde **83I** (2 mg, 2%).

### Competing Experiments between Dithiane **80a** and Dithiolane **81a**.

To the mixture of **80a** (231 mg, 1.0 mmol) and **81a** (217 mg, 1.0 mmol) in MeCN (5.29 ml) and H<sub>2</sub>O (0.21 ml), was added a solution of DDQ (272 mg, 1.2 mmol) in MeCN (1.5 ml) under nitrogen. After stirring at room temperature for 3 h, the mixture was worked up as described above to give **80a** (27 mg, 12%), **81a** (195 mg, 90%), and **83a** (113 mg, 80%).

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## Chapter 7. The Reactions of Dithioacetals Derived from Cinnamaldehydes with DDQ

Deprotection of dithioacetals using oxidizing agents has been extensively investigated<sup>1)</sup> and a variety of dithioacetals including 2-styryl-1,3-dithiane (**104c**) ( $R = Ph$ ) were converted into the corresponding carbonyl compounds in good yields<sup>2-4)</sup>. In Chapter 6, deprotection of dithioacetals using DDQ in aqueous MeCN was described.<sup>5,6)</sup> In the course of the investigations, the unexpected product, benzaldehyde (**107c**) was obtained from the hydrolysis of dithiane **104c** with DDQ. In this chapter, the author describes the novel reactions between dithioacetals derived from cinnamaldehydes with DDQ.

1,3-Dithiane **104c** was treated with DDQ in MeCN-H<sub>2</sub>O (97:3) at room temperature for 15 minutes under nitrogen in the dark. Two equiv. of DDQ were necessary for the complete conversion of **104c** and changed to DDQH<sub>2</sub> quantitatively. Surprisingly, benzaldehyde (**107c**) (41%) was obtained with a small amount of cinnamaldehyde (**108c**) (5%) (Table 7-1, Run 6). Similarly, various dithianes **104a-e** reacted with DDQ in aqueous solvents to give benzaldehydes **107**, small amounts of cinnamaldehydes **108**, and rearranged thioesters **109** (entries 1-13). When 2-(2,2-diphenylvinyl)-1,3-dithiane **110** was treated with DDQ in MeCN-H<sub>2</sub>O (97:3) for 1 h, deprotection occurred exclusively to give 3,3-diphenyl-2-propenal (90%). In CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O (97:3) for 24 hours, benzophenone (4%) was produced with the deprotected product (58%). In the cases of dithiolanes **105**, benzaldehydes **107** and 2-phenacylidene-1,3-dithiolanes **88** were obtained together with small amounts of cinnamaldehydes **108** (entries 14-19). From the reactions of cinnamaldehydes diphenyl dithioacetal **106**, benzaldehydes **107**, cinnamaldehydes **108**, and diphenyl disulfide (9-79%) were isolated (entries 20-25). In the case of **106c**, some by-products, *i.e.*, (*E*)-3-phenyl-3-phenylsulfanyl-2-propenal (**111**) (14%), (*E*)-1-phenyl-3-phenylsulfanyl-2-propen-1-one (**112a**) (6%),

(*Z*)-**112b** (8%), and *S*-phenyl 3-phenyl-2-propenethioate (**113**) (14%), were formed together with the deprotected **108c** (49%) (entry 22). Only a complex mixture was obtained from the reactions of 2-alkenal dithioacetals **104-106** ( $R = \text{CH}_3$  and  $n\text{-C}_9\text{H}_{19}$ ).

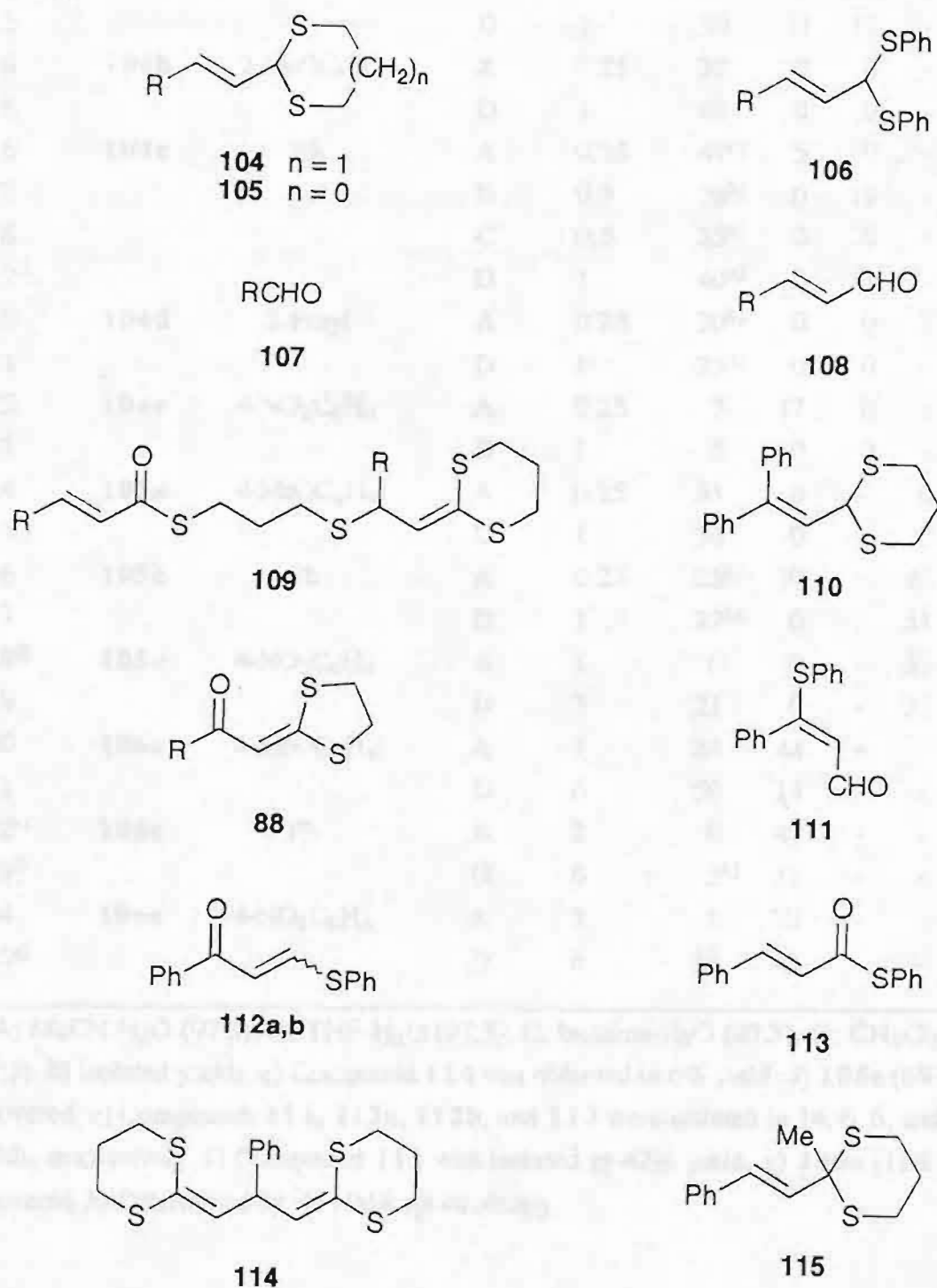


Figure 7-1.

Table 7-1. The Reactions of Dithioacetals **104-106** with DDQ in Aqueous Solvents

Entry	Substrate	R	Solvent <sup>a)</sup>	Time h	Product /% <sup>b)</sup>			
					107	108	109	88
1	<b>104a</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	A	0.25	38	0	18	-
2			C	0.25	33	0	10	-
3			D	1	50	0	17	-
4	<b>104b</b>	2-MeOC <sub>6</sub> H <sub>4</sub>	A	0.25	38	0	0	-
5			D	1	48	0	0	-
6	<b>104c</b>	Ph	A	0.25	41 <sup>h)</sup>	5	0	-
7			B	0.2	23 <sup>h)</sup>	0	19	-
8			C	0.5	25 <sup>h)</sup>	0	0	-
9 <sup>c)</sup>			D	1	40 <sup>h)</sup>	0	11	-
10	<b>104d</b>	2-Furyl	A	0.25	20 <sup>h)</sup>	0	0	-
11			D	1	25 <sup>h)</sup>	0	0	-
12	<b>104e</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	A	0.25	7	17	0	-
13			D	1	5	0	0	-
14	<b>105a</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	A	0.25	33	0	-	0
15			D	1	34	0	-	0
16	<b>105c</b>	Ph	A	0.25	25 <sup>h)</sup>	10	-	42
17			D	1	22 <sup>h)</sup>	0	-	31
18 <sup>d)</sup>	<b>105e</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	A	1	0	7	-	37
19			D	3	21	0	-	33
20	<b>106a</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	A	1	24	48	-	-
21			D	6	50	14	-	-
22 <sup>e)</sup>	<b>106c</b>	Ph	A	2	0	49	-	-
23 <sup>f)</sup>			D	6	2 <sup>h)</sup>	11	-	-
24	<b>106e</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	A	2	0	73	-	-
25 <sup>g)</sup>			D	6	18	43	-	-

a) A; MeCN-H<sub>2</sub>O (97:3), B; THF-H<sub>2</sub>O (97:3), C; benzene-H<sub>2</sub>O (97:3), D; CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O (97:3). b) Isolated yields. c) Compound **114** was obtained in 6% yield. d) **105e** (6%) was recovered. e) Compounds **111**, **112a**, **112b**, and **113** were isolated in 14, 6, 8, and 14% yields, respectively. f) Compound **111** was isolated in 42% yield. g) **106e** (11%) was recovered. h) Determined by <sup>1</sup>H NMR spectroscopy.



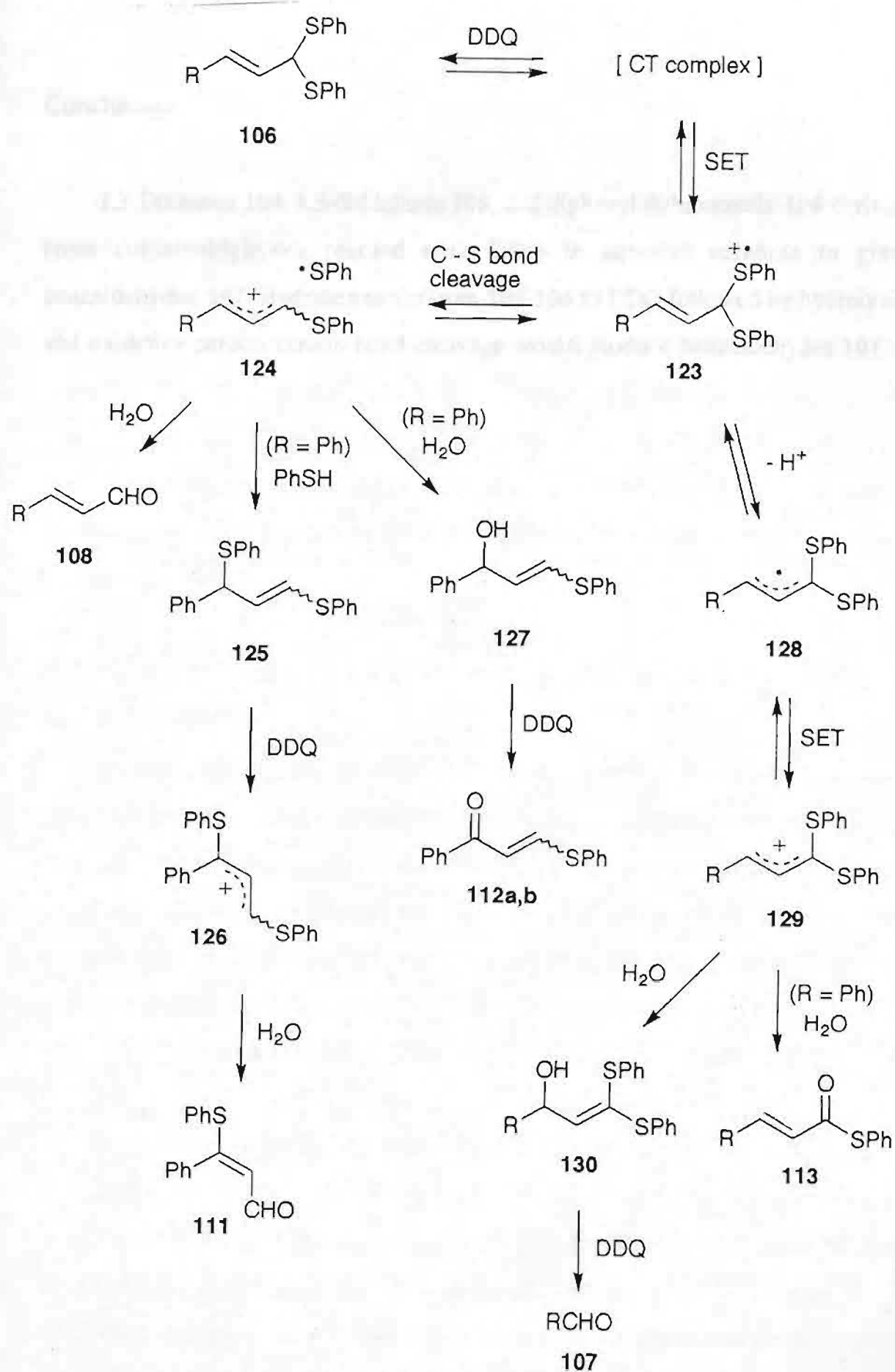
Although the exact reaction path is not clear now, the plausible mechanisms of the formation of benzaldehyde **107** are shown in Schemes 7-1 and 7-2. Hydride transfer from **104** or **105** to DDQ, which consists of consecutive SET, proton transfer, and second SET steps, would generate cation **118** which is hydrolyzed to give **119**. Oxidative carbon-carbon bond cleavage of **119** induced by DDQ would produce benzaldehyde **107**. On the other hand, hydrolysis of cation **118** would afford **122**. The resulting thiol **122** is converted into **109** by the reaction with stabilized cation **118** rather than oxidized to disulfide.<sup>6)</sup> 2-Phenacylidene-1,3-dithiolanes **88** would be produced by hydride transfer from **119** to DDQ.



These mechanisms would be supported by the following results. (i) A dark red coloration due to the formation of CT complex was observed during the reaction;  $\lambda_{\text{max}}$  (CT) = 547 and 587 nm for **104c**, 543 and 583 nm for **105c**, and 542 and 580 nm for **106c**. (ii) Bis(dithiane) **114** (6%), which might be produced via addition of radical **121** to the starting **104**, was isolated from the reaction of **104c** with DDQ in  $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$  (97:3) (Run 9). (iii) Dithioacetals bearing a methoxy group on the benzene ring increased the yields of benzaldehydes **107**, since the benzylic cation **118** was stabilized. In contrast, a nitro group suppressed the formation of **107** markedly. (iv) When 2-methyl-2-styryl-1,3-dithiane **115** was treated with DDQ for 15 minutes in  $\text{MeCN-H}_2\text{O}$  (97:3), only deprotection occurred (77%). In  $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$  (97:3), no reaction was observed. These results suggest that hydride transfer from the 2-position of 1,3-dithiane **104** to DDQ would be involved in the first stage of benzaldehyde formation. (v) Compound **88** was stable under these conditions and was not converted into benzaldehyde **107**.

A plausible mechanism for the formation of compounds **111-113** is shown in Scheme 7-2. The first step is a SET process from **106** to DDQ. The subsequent steps of the resulting cation radical **123** involving carbon-sulfur bond cleavage, the attack by benzenethiol<sup>7)</sup> which is generated during the reaction, hydride transfer, and the attack by water, lead to **111**. Hydrolysis of **124** followed by further oxidation by DDQ would form **112a,b**. The sequence of deprotonation, SET, and hydrolysis steps from **123** would lead to thioester **113**.





Scheme 7-2.

## Conclusions

1,3-Dithianes **104**, 1,3-dithiolanes **105**, and diphenyl dithioacetals **106** derived from cinnamaldehydes reacted with DDQ in aqueous solvents to give benzaldehydes **107**. Hydride transfer from **104-106** to DDQ followed by hydrolysis and oxidative carbon-carbon bond cleavage would produce benzaldehydes **107**.

## Experimental

All melting points are uncorrected. Column chromatography was performed on Merck silica gel 60 (70-230 mesh). DDQ was recrystallized from benzene-hexane. The IR spectra were recorded on a Hitachi I-3000 spectrophotometer.  $^1\text{H}$  (90 MHz, 60 MHz) and  $^{13}\text{C}$  (22.49 MHz) NMR spectra were measured on a JEOL JNM-FX 90Q or a Hitachi R-24B spectrometer using tetramethylsilane as an internal standard. The UV spectra were recorded on a Hitachi Model 320 spectrophotometer. Dithioacetals **104-106**, **110**, and **115** were synthesized according to the literature procedure.<sup>8)</sup> All reactions were carried out under nitrogen in the dark.

General Procedure for the Reaction of Dithioacetals **104-106** with DDQ in MeCN-H<sub>2</sub>O (97:3).

To a mixture of dithiane **104a** (252 mg, 1.0 mmol) in MeCN (3.28 ml) and H<sub>2</sub>O (0.57 ml) was added a solution of DDQ (454 mg, 2.0 mmol) in MeCN (15.15 ml). After stirring at room temperature for 15 min, the mixture was quenched with saturated sodium hydrogencarbonate (50 ml) and extracted with ether. The extracts were washed with water, dried, and evaporated and the residue was chromatographed on silica gel with 10:1 hexane-acetone to give benzaldehyde **107a** (52 mg, 38%) and thioester **109a** (46 mg, 18%) (Table 7-1, entry 1).

General Procedure for the Reaction of Dithioacetals **104-106** with DDQ in CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O (97:3).

To a mixture of dithiane **104a** (252 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.28 ml) and H<sub>2</sub>O (0.57 ml) was added a solution of DDQ (454 mg, 2.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15.15 ml). After stirring at room temperature for 1 h, the mixture was worked up as described above except for extraction with dichloromethane to give benzaldehyde



**107a** (68 mg, 50%) and thioester **109a** (44 mg, 17%) (Table 7-1, entry 3).

Thioester **109a** (R = 4-MeOC<sub>6</sub>H<sub>4</sub>).

Colorless oil; IR (neat) 1666 cm<sup>-1</sup> (COS) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60 MHz):  $\delta$  = 1.75-2.34 (4H, m, CH<sub>2</sub>), 2.56 (2H, t, J = 7.0 Hz, CH<sub>2</sub>), 2.88 (4H, t, J = 6.0 Hz, CH<sub>2</sub>), 3.09 (2H, t, J = 7.0 Hz, CH<sub>2</sub>), 3.73 (3H, s, OCH<sub>3</sub>), 3.80 (3H, s, OCH<sub>3</sub>), 5.06 (1H, d, J = 10.1 Hz, CH), 6.11 (1H, d, J = 10.1 Hz, CH=C), 6.55 (1H, d, J = 15.8 Hz, ArCH=CH), and 6.62-7.83 (9H, m, ArH and ArCH=CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.49 MHz)  $\delta$  = 24.8 (t), 27.9 (t), 29.6 (t), 29.6 (t), 29.9 (t), 30.3 (t), 46.7 (d), 55.2 (q), 55.3 (q), 114.0 (d), 114.4 (d), 122.7 (d), 128.1 (s), 128.7 (d), 130.0 (d), 131.8 (s), 131.9 (s), 132.0 (d), 140.1 (d), 158.7 (s), 161.6 (s), and 189.4 (s). Found: C, 60.43; H, 5.97%. Calcd for C<sub>26</sub>H<sub>30</sub>O<sub>3</sub>S<sub>4</sub>: C, 60.20; H, 5.83%.

Thioester **109c** (R = Ph).

Colorless needles, mp 87-88 °C (from benzene-hexane) IR (KBr): 1674 (COS), 1656 cm<sup>-1</sup> (C=C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 1.79-2.30 (4H, m, CH<sub>2</sub>), 2.58 (2H, t, J = 7.0 Hz, CH<sub>2</sub>), 2.88 (4H, t, J = 6.0 Hz, CH<sub>2</sub>), 3.10 (2H, t, J = 7.0 Hz, CH<sub>2</sub>), 5.10 (1H, d, J = 10.1 Hz, CH), 6.14 (1H, d, J = 10.1 Hz, CH=C), 6.68 (1H, d, J = 15.8 Hz, PhCH=CH), 7.14-7.60 (10H, m, ArH), and 7.60 (1H, d, J = 15.8 Hz, PhCH=CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.49 MHz)  $\delta$  = 24.8 (t), 28.0 (t), 29.5 (t), 29.6 (t), 29.9 (t), 30.4 (t), 47.6 (d), 125.1 (d), 127.3 (d), 127.7 (d), 128.3 (d), 128.6 (d), 128.9 (d), 129.8 (s), 130.5 (d), 131.4 (d), 134.2 (s), 140.2 (s), 140.4 (d), and 189.3 (s). Found: C, 63.10; H, 5.98%. Calcd for C<sub>24</sub>H<sub>26</sub>OS<sub>4</sub>: C, 62.84; H, 5.71%.

2-(4-Nitrophenacylidene)-1,3-dithiolane (**88e**).

Yellow prisms, mp 230-231 °C (from acetone); IR (KBr) 1620 (C=O), 1518, 1346 cm<sup>-1</sup> (NO<sub>2</sub>); <sup>1</sup>H NMR (CD<sub>3</sub>SOCD<sub>3</sub>, 60 MHz)  $\delta$  = 3.53 (4H, s, CH<sub>2</sub>), 7.55 (1H, s, C=CH), and 7.28 (4H, s, ArH). Found: C, 49.70; H, 3.66%. Calcd for C<sub>11</sub>H<sub>9</sub>NO<sub>3</sub>S<sub>2</sub>:

C, 49.42; H, 3.39%.

(*E*)-3-Phenyl-3-phenylsulfanyl-2-propenal (**111**).<sup>9)</sup>

Yellow prisms, mp 134-135 °C (from hexane); IR (KBr) 1660 cm<sup>-1</sup> (CHO); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60 MHz) δ = 5.68 (1H, d, J = 7.9 Hz, 2-H), 7.48 (10H, s, ArH), and 9.27 (1H, d, J = 7.9 Hz, CHO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.49 MHz) δ = 123.5 (d), 127.7 (s), 128.5 (d), 129.0 (d), 129.4 (d), 129.9 (d), 130.1 (d), 134.6 (s), 135.2 (d), 168.3 (s), and 189.3 (d).

(*E*)-1-Phenyl-3-phenylsulfanyl-2-propen-1-one (**112a**).<sup>10)</sup>

Pale yellow needles, mp 71-73 °C (from hexane); IR (KBr) 1644 cm<sup>-1</sup> (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz) δ = 6.85 (1H, d, J = 14.8 Hz, 2-H), 7.35-7.58 (8H, m, ArH), 7.79-7.90 (2H, m, ArH), and 8.02 (1H, d, J = 14.8 Hz, 3-H).

(*Z*)-1-Phenyl-3-phenylsulfanyl-2-propen-1-one (**112b**).<sup>10)</sup>

Pale yellow needles, mp 79-80 °C (from hexane); IR (KBr) 1638 cm<sup>-1</sup> (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz) δ = 7.14 (1H, d, J = 9.7 Hz, 2-H), 7.33-7.60 (8H, m, ArH), 7.58 (1H, d, J = 9.7 Hz, 3-H), and 7.95-8.05 (2H, m, ArH).

*S*-Phenyl 3-phenyl-2-propenethioate (**113**).<sup>11)</sup>

Yellow needles, mp 90-91 °C (from hexane) (*lit.*, mp 85-86 °C); IR (KBr) 1682 cm<sup>-1</sup> (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60 MHz): δ = 6.77 (1H, d, J = 15.8 Hz, 2-H), 7.35-7.59 (10H, m, ArH), and 7.68 (1H, d, J = 15.8 Hz, 3-H).

1,3-Bis(1,3-dithian-2-ylidene)-2-phenylpropane (**114**).

Colorless prisms, mp 129-130 °C (from benzene-hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60 MHz) δ = 1.92-2.40 (4H, m, CH<sub>2</sub>), 2.90 (8H, t, J = 6.0 Hz, CH<sub>2</sub>), 5.17 (1H, dd, J = 9.0 and 9.0 Hz, CH), 6.02 (2H, d, J = 9.0 Hz, C=CH), and 7.21 (5H, s, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.49 MHz) δ = 25.0 (t), 29.6 (t), 30.1 (t), 45.2 (d), 126.4 (d), 127.4



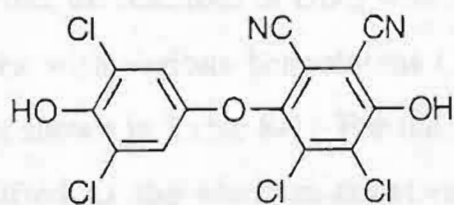


## References

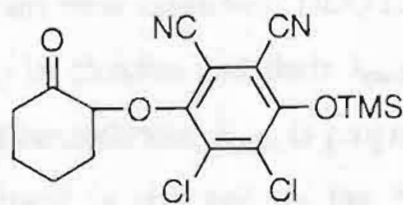
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## Chapter 8. The Reactions of DDQ with Benzofurans and Indoles

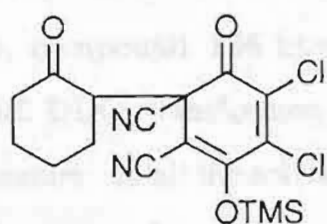
DDQ is known to form CT complex with many aromatic hydrocarbons, heterocycles, and olefins.<sup>1,2)</sup> Among them, some compounds afford substitution products with DDQ via CT complex. For instance, Becker<sup>3)</sup> isolated carbon-oxygen adduct **131** in the reaction of DDQ with 2,6-dichlorophenol. Bhattacharya and co-workers<sup>4)</sup> have reported that carbon-oxygen adduct **132** and carbon-carbon adduct **133** were produced by the reaction of DDQ with (trimethylsiloxy)cyclohexene and that relative yield of **133** increased with increasing solvent polarity. Carbon-carbon adducts were often isolated in the reaction of quinones.<sup>5)</sup> In this chapter, the author reports that DDQ reacts with 6-methoxy-3-methylbenzofuran (**136**) to give carbon-oxygen adduct **142**, while DDQ reacts with indoles **145-149**, which are heterocyclic analogs of benzofuran, to yield carbon-carbon adducts **150-154**, respectively. Solvent effects of these reactions are also described.



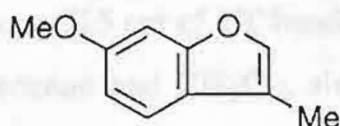
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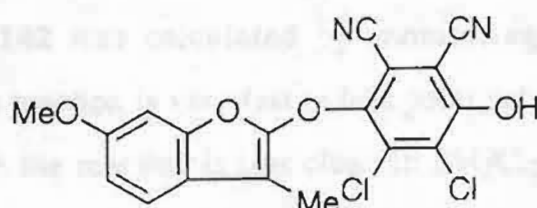
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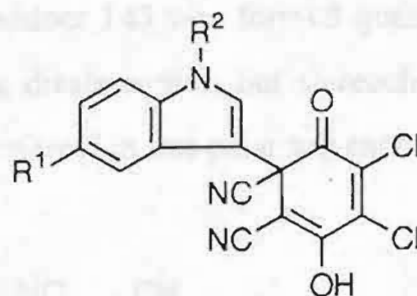
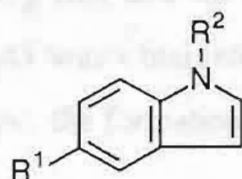
133



136



142

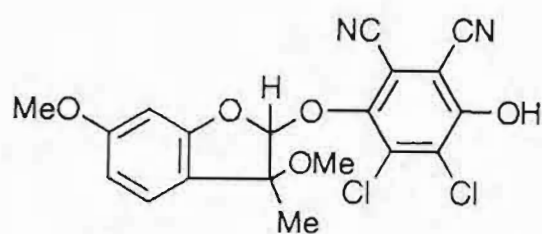


	R <sup>1</sup>	R <sup>2</sup>	
145	H	H	150
146	Cl	H	151
147	Br	H	152
148	OMe	H	153
149	H	Me	154

Figure 8-1.



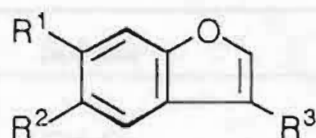
First, the reactions of DDQ with benzofurans were examined. DDQ forms CT complex with various benzofurans (**134-141**) in dioxane and their  $\lambda_{\text{max}}$  of CT band is shown in Table 8-1. For the series of benzofurans,  $\lambda_{\text{max}}$  is progressively red-shifted as the electron-donative substituent is attached on the benzene ring.<sup>6,7)</sup> CT band of 6-methoxy-3-methylbenzofuran (**136**) has an absorption maximum at 715 nm, which is the longest wavelength among these benzofurans. In benzene, compound **136** immediately formed intensely green-colored CT complex with DDQ, transformed to carbon-oxygen adduct **142** within 5 min at room temperature. In all the solvents examined, adduct **142** was isolated. Solvent effects on the adduct formation were examined and the results are summarized in Table 8-2. Conversion of **136** to **142** was calculated by monitoring the absorbance at 715 nm of CT band. The reaction is very fast in less polar solvents such as benzene and  $\text{CH}_2\text{Cl}_2$ , although the reaction is less clean in  $\text{CH}_2\text{Cl}_2$ . In more polar solvents such as THF and dioxane, the reaction proceeds more slowly. In  $\text{MeNO}_2$  and  $\text{MeCN}$ , only polymeric materials were obtained. In  $\text{MeOH}$ , the reaction is very fast and the methanol adduct **143** was formed quantitatively. Compound **143** was obtained as a single diastereomer, but stereochemistry is unknown. Thus, the formation of **142** is preferred in less polar solvents.



**143**

Figure 8-2.

Table 8-1. Absorption Maxima of the CT Complex between DDQ and Benzofurans in Dioxane<sup>a)</sup>



Benzofuran	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	$\lambda_{\text{max}}$ of CT complex / nm
134	Cl	H	Me	500
135	Me	H	Me	625
136	MeO	H	Me	715
137	H	Cl	Me	510
138	H	Me	Me	550
139	H	MeO	Me	605
140	H	H	Me	510
141	MeO	H	H	675

a) Concentration;  $4.1 \times 10^{-2}$  M

Table 8-2. Reactions of DDQ with 6-Methoxy-3-methylbenzofuran (**136**) in Various Solvents<sup>a)</sup>

Entry	Solvent	Conv. <sup>b)</sup> /%
1	CH <sub>2</sub> Cl <sub>2</sub>	100
2	Benzene	90
3	THF	37
4	Dioxane	2
5	MeNO <sub>2</sub>	100 <sup>c)</sup>
6	MeCN	100 <sup>c)</sup>
7	MeOH	100 <sup>d)</sup>

a) Reaction conditions; **136** 1 mmol, DDQ 1.05 mmol, reaction time 15 min.

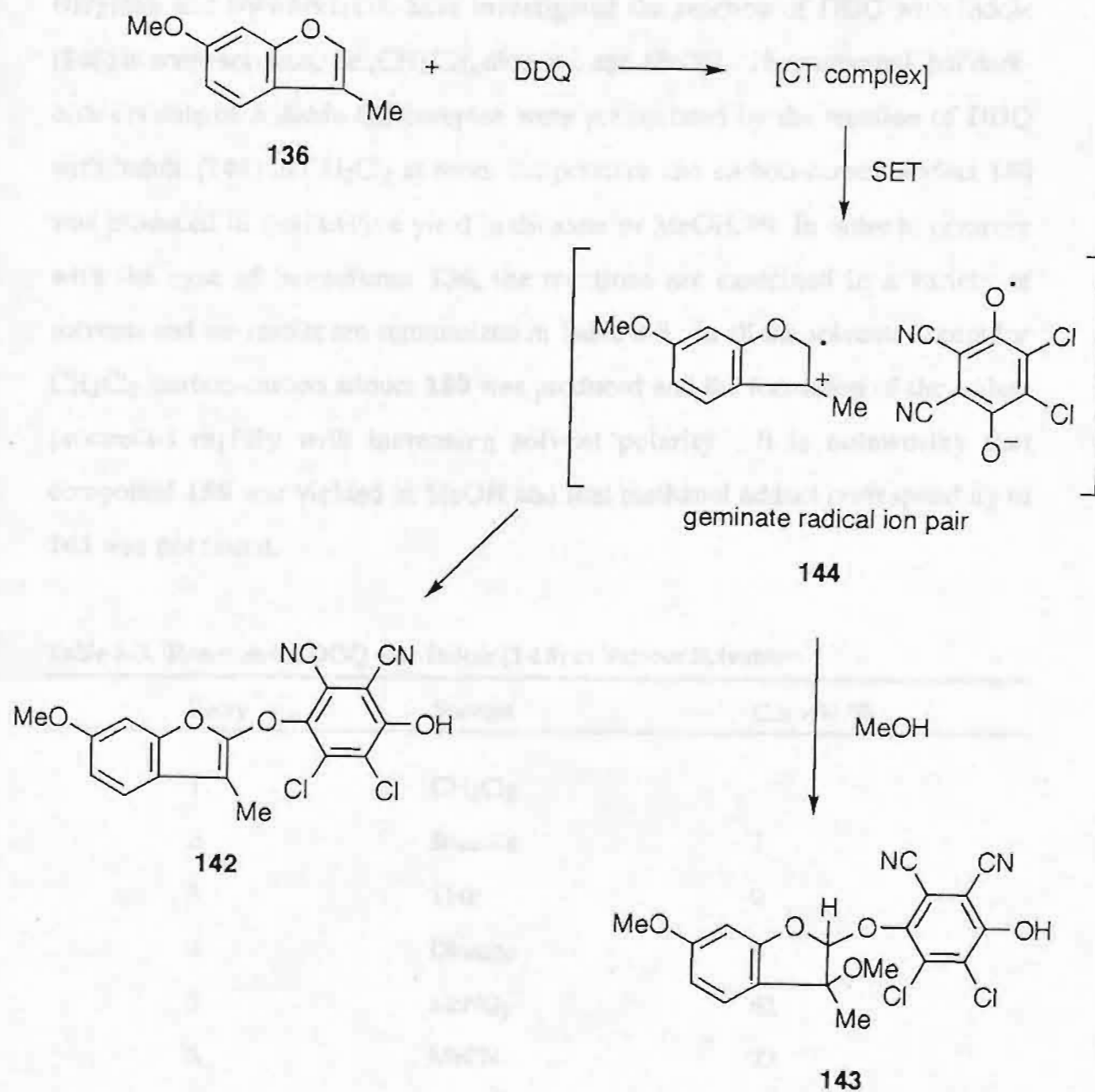
b) Conversion was calculated by monitoring the absorbance at 715 nm of CT band.

c) Polymeric materials were obtained. d) **143** was obtained in 99% yield.



The formation of the products **142** and **143** is explained by a SET mechanism between DDQ and benzofuran **136** as shown in Scheme 8-1. Many examples are known affording carbon-oxygen adduct via a SET mechanism in photochemical<sup>8)</sup> or thermal<sup>9)</sup> reactions of quinones. In less polar solvents, coupling of the geminate radical ion pair in the solvent cage is favored. In more polar solvents, which encourage the radical ion pair to escape from the solvent cage, the radical coupling is suppressed.<sup>10-12)</sup> When the reaction was carried out in MeOH, benzofuran cation radical was immediately trapped by MeOH before escape from the solvent cage and hence the reaction was accelerated.<sup>13)</sup>





Scheme 8-1.

Next, the reactions of DDQ with some indole derivatives were explored. Bergman and co-workers<sup>14)</sup> have investigated the reaction of DDQ with indole (**145**) in some solvents, *i.e.*, CH<sub>2</sub>Cl<sub>2</sub>, dioxane, and MeOH. They reported that dark-blue crystals of a stable CT complex were precipitated by the reaction of DDQ with indole (**145**) in CH<sub>2</sub>Cl<sub>2</sub> at room temperature and carbon-carbon adduct **150** was produced in quantitative yield in dioxane or MeOH.<sup>14)</sup> In order to compare with the case of benzofuran **136**, the reactions are examined in a variety of solvents and the results are summarized in Table 8-3. In all the solvents except for CH<sub>2</sub>Cl<sub>2</sub>, carbon-carbon adduct **150** was produced and the formation of the adduct proceeded rapidly with increasing solvent polarity. It is noteworthy that compound **150** was yielded in MeOH and that methanol adduct corresponding to **143** was not found.

Table 8-3. Reactions of DDQ with Indole (**145**) in Various Solvents<sup>a)</sup>

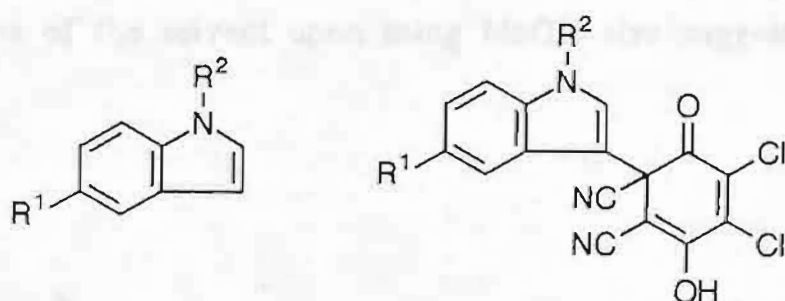
Entry	Solvent	Conv. <sup>b)</sup> /%
1	CH <sub>2</sub> Cl <sub>2</sub>	- c)
2	Benzene	3
3	THF	9
4	Dioxane	8
5	MeNO <sub>2</sub>	62
6	MeCN	72
7	MeOH	10

a) Reaction conditions; **145** 1 mmol, DDQ 1.05 mmol, reaction time 60 min.

b) Conversion was calculated by monitoring the absorbance at 592 nm of CT band. c) The dark-blue precipitates of CT complex were yielded.



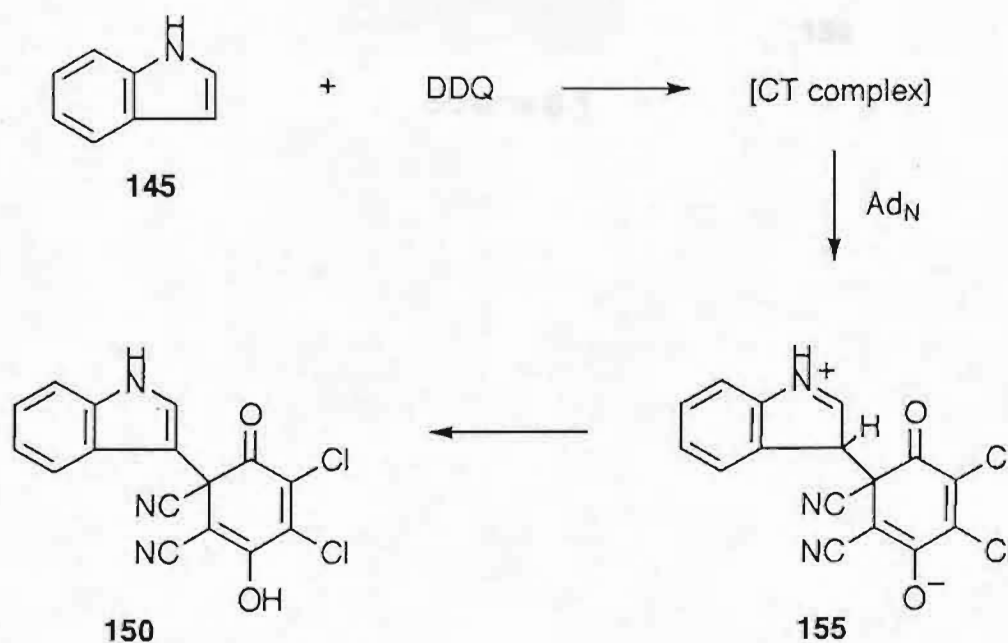
The other indole derivatives **146-149** afforded carbon-carbon adducts **151-154** in dioxane, respectively (Figure 8-3). As substituent on benzene ring is more electron-donative, the reaction proceeded much rapidly. The reaction of 2-methylindole,<sup>14)</sup> 3-methylindole, or 5-methoxy-2-methylindole with DDQ in various solvents afforded only polymeric materials.



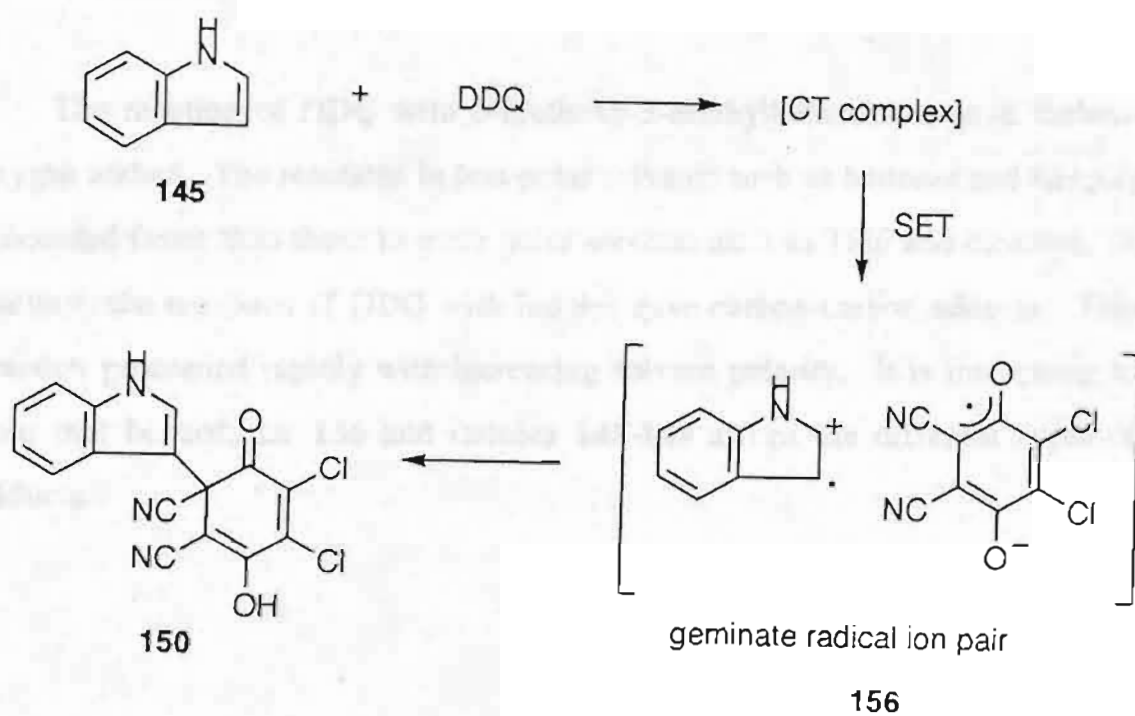
	R <sup>1</sup>	R <sup>2</sup>	
<b>145</b>	H	H	<b>150</b> ( 24 h 98%)
<b>146</b>	Cl	H	<b>151</b> (120 h 95%)
<b>147</b>	Br	H	<b>152</b> (120 h 100%)
<b>148</b>	OMe	H	<b>153</b> ( 2 h 100%)
<b>149</b>	H	Me	<b>154</b> (24 h 100%)

Figure 8-3.

Carbon-carbon adduct **150** is considered to be formed by a nucleophilic attack of indole on DDQ (Scheme 8-2).<sup>15,16</sup> However, a SET mechanism between indole and DDQ shown in Scheme 8-3 cannot be ruled out. Carbon-carbon adducts are often produced via a SET mechanism. The formation of compound **133** was explained by a SET mechanism.<sup>4</sup> A large solvent effect in the reactions of indole with DDQ suggests that carbon-carbon adduct **150** is formed by a different mechanism from that of the formation of carbon-oxygen adduct **142**. No incorporation of the solvent upon using MeOH also suggests a different mechanism.



Scheme 8-2.



Scheme 8-3.



## Conclusions

The reaction of DDQ with 6-methoxy-3-methylbenzofuran gave carbon-oxygen adduct. The reactions in less polar solvents such as benzene and  $\text{CH}_2\text{Cl}_2$  proceeded faster than those in more polar solvents such as THF and dioxane. In contrast, the reactions of DDQ with indoles gave carbon-carbon adducts. This reaction proceeded rapidly with increasing solvent polarity. It is interesting to note that benzofuran **136** and indoles **145-149** afford the different types of adducts.

## Experimental

All melting points are uncorrected. Column chromatography was performed on silica gel (Wakogel C-200).  $\text{CH}_2\text{Cl}_2$ ,  $\text{C}_6\text{H}_6$ , and MeCN were distilled over  $\text{P}_2\text{O}_5$ . THF and dioxane were refluxed with sodium for 1 day and distilled. MeOH was dried by Molecular Sieves 4A and distilled. DDQ was recrystallized from benzene-hexane. IR spectra were determined on a Jasco IRA-2 or a Hitachi I-3000 spectrophotometer.  $^1\text{H}$  (90 MHz, 60 MHz) and  $^{13}\text{C}$  (22.49 MHz) NMR spectra were determined on a JEOL JNM-FX 90Q or a Hitachi R-24B spectrometer, using  $\text{Me}_4\text{Si}$  as an internal standard. UV-VIS spectra were recorded on a Hitachi Model 320 spectrophotometer.

### Reaction of 6-Methoxy-3-methylbenzofuran (**136**) with DDQ in Benzene.

A solution of DDQ (294 mg, 1.29 mmol) in dry benzene (15 ml) was added to a solution of **136** (200 mg, 1.23 mmol) in dry benzene (15 ml) at room temperature under nitrogen. After stirring for 15 min, the mixture was evaporated. The residue was chromatographed and eluted with benzene-acetone (1:4) to give **142** (466 mg, 97%) as yellow needles; Mp 197-198 °C (from acetone); IR (KBr) 3260 (broad, OH) and 2240  $\text{cm}^{-1}$  (CN);  $^1\text{H}$  NMR ( $\text{CD}_3\text{SOCD}_3$ , 90 MHz)  $\delta$  = 2.14 (3H, s, 3'-Me), 3.78 (3H, s, OMe), 6.88 (1H, dd,  $J$  = 9.0 and 2.0 Hz, ArH), 7.07 (1H, d,  $J$  = 2.0 Hz, ArH), 7.40 (1H, d,  $J$  = 9.0 Hz, ArH), and 7.73 (1H, br s, OH);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{SOCD}_3$ , 22.49 MHz)  $\delta$  = 6.2 (q), 55.6 (q), 93.0 (s), 96.2 (d), 102.6 (s), 108.1 (s), 111.7 (d), 111.8 (s), 113.1 (s), 119.5 (d), 122.4 (s), 129.7 (s), 132.7 (s), 145.2 (s), 149.0 (s), 152.0 (s), 156.2 (s), and 157.3 (s). Found: C, 55.25; H, 2.79%. Calcd for  $\text{C}_{18}\text{H}_{10}\text{N}_2\text{O}_4\text{Cl}_2$ : C, 55.53; H, 2.59%.

### Reaction of **136** with DDQ in Methanol.

A solution of DDQ (294 mg, 1.29 mmol) in dry methanol (15 ml) was added



to a solution of **136** (200 mg, 1.23 mmol) in dry methanol (15 ml) at room temperature under nitrogen. After stirring for 15 min, the mixture was evaporated at 0 °C to give **143** (554 mg, 99%) as colorless needles (containing methanol of crystallization). The analytical sample was recrystallized from methanol carefully. This compound was converted into **142** on heating above mp. Mp 91-93 °C (dec.); IR (KBr) 3470 (broad, OH) and 2250  $\text{cm}^{-1}$  (CN);  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ , 60 MHz)  $\delta$  = 1.80 (3H, s, 3'-Me), 3.10 (3H, s, 3'-OMe), 3.81 (3H, s, 6'-OMe), 5.72 (1H, br s, OH), 5.97 (1H, s, 2'-H), 6.56-6.79 (2H, m, ArH), and 7.35 (1H, dd,  $J$  = 8.0 and 1.0 Hz, ArH);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{COCD}_3$ , 22.49 MHz)  $\delta$  = 17.7 (q), 50.8 (q), 56.0 (q), 85.6 (s), 98.7 (d), 103.5 (s), 109.0 (d), 111.9 (s), 112.6 (s), 113.1 (s), 113.7 (d), 120.1 (s), 125.8 (d), 129.2 (s), 135.6 (s), 148.9 (s), 155.4 (s), 161.3 (s), and 163.5 (s). Found: C, 52.93; H, 4.26%. Calcd for  $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_5\text{Cl}_2 \cdot \text{CH}_3\text{OH}$ : C, 53.00, H, 4.00%.

#### Indole-DDQ CT complex.<sup>14)</sup>

A solution of DDQ (119 mg, 0.52 mmol) in dry dichloromethane (6.1 ml) was added to a solution of indole (**145**) (59 mg, 0.50 mmol) in dry dichloromethane (6.1 ml) at room temperature under nitrogen. The solution was stirred for 15 min. The dark blue crystals formed were collected by filtration to give the CT complex (169 mg, 98%). The complex was recrystallized from dichloromethane. Mp 220-230 °C (dec.); IR (KBr) 3412 (NH), 2232 (CN), and 1680  $\text{cm}^{-1}$  (CO).

#### Reaction of Indole (**145**) with DDQ in Dioxane.

A solution of DDQ (477 mg, 2.10 mmol) in dry dioxane (22 ml) was added to a solution of **145** (234 mg, 2.00 mmol) in dry dioxane (22 ml) at room temperature under nitrogen. After 24 h, the solvent was removed under reduced pressure to give **150** (847 mg, 98%) as orange-red prisms (containing dioxane of crystallization). The analytical sample was recrystallized from ether-hexane. Mp



130-133 °C (*lit.*<sup>14</sup>) 130-135 °C); IR (KBr) 3424 (NH), 3115 (broad, OH), 2224 (CN), and 1700 cm<sup>-1</sup> (CO); <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>, 60 MHz) δ = 7.10-7.94 (5H, ArH), 8.12 (1H, br s, OH), and 10.70 (1H, br s, NH); <sup>13</sup>C NMR (CD<sub>3</sub>COCD<sub>3</sub>, 22.49 MHz) δ = 51.8 (s), 105.2 (s), 113.3 (d), 114.7 (s), 115.6 (s), 120.0 (d), 121.4 (d), 122.2 (s), 123.7 (d), 124.4 (s), 125.1 (s), 125.5 (d), 138.3 (s), 143.8 (s), 156.0 (s), and 179.1 (s).

Spectral data and elemental analyses of C-C adducts **151-154** are as follows.

**151**; brown prisms, mp 129-132 °C (dec.) (from ether-hexane); IR (KBr) 3440 (NH), 3184 (broad, OH), 2224 (CN), and 1714 cm<sup>-1</sup> (CO); <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>, 60 MHz) δ = 6.01 (1H, br s, OH), 7.03 (4H, m, ArH), and 11.00 (1H, br s, NH). Found: C, 50.48; H, 1.85%. Calcd for C<sub>16</sub>H<sub>6</sub>N<sub>3</sub>O<sub>2</sub>Cl<sub>3</sub>: C, 50.76; H, 1.60%.

**152**; brown prisms, mp 143-148 °C (dec.) (from ether-hexane); IR (KBr) 3444 (NH), 3220 (broad, OH), 2224 (CN), and 1706 cm<sup>-1</sup> (CO); <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>, 60 MHz) δ = 6.62 (1H, br s, OH), 7.27 (4H, m, ArH), and 10.98 (1H, br s, NH). Found: C, 45.69; H, 1.64%. Calcd for C<sub>16</sub>H<sub>6</sub>N<sub>3</sub>O<sub>2</sub>Cl<sub>2</sub>Br: C, 45.43; H, 1.43%.

**153**; yellow prisms, mp 117-122 °C (dec.) (from ether-hexane); IR (KBr) 3432 (NH), 3300 (broad, OH), 2224 (CN), and 1706 cm<sup>-1</sup> (CO); <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>, 60 MHz) δ = 3.83 (3H, s, Me), 5.69 (1H, br s, OH), 6.90 (1H, dd, J = 9.0 and 2.0 Hz, ArH), 7.20-7.70 (3H, m, ArH), and 10.70 (1H, br s, NH). Found: C, 54.37; H, 2.60%. Calcd for C<sub>17</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>Cl<sub>2</sub>: C, 54.57; H, 2.42%.

**154**; orange-red prisms, mp 134-138 °C (dec.) (from ether-hexane) (*lit.*<sup>14</sup>) 130-135 °C); IR 3220 (broad, OH), 2224 (CN), and 1710 cm<sup>-1</sup> (CO); <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>, 60 MHz) δ = 3.79 (3H, s, 1'-Me), 6.20 (1H, br s, OH), and 7.10-8.00 (5H, m, ArH).

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## Chapter 9. Dibenzofuran Formation from the Reactions of 1-Cyclohexenyloxydibutylboranes with DDQ

Oxidation of cyclohexanones to cyclohexenones *via* the reactions of silyl enol ethers with DDQ is one of the important synthetic transformations.<sup>1)</sup> Recently, the intermediacy of carbon-oxygen adduct **132** and carbon-carbon adduct **133** was reported in the reaction of **157** with DDQ.<sup>2)</sup> In connection with these reactions, it occurred to use vinyloxyboranes<sup>3)</sup> instead of silyl enol ethers. In this chapter, new dibenzofuran formation by the reactions of 1-cyclohexenyloxydibutylboranes with DDQ is reported.

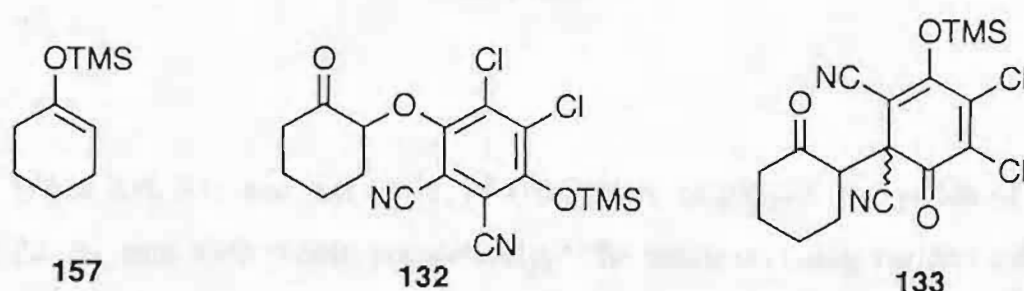
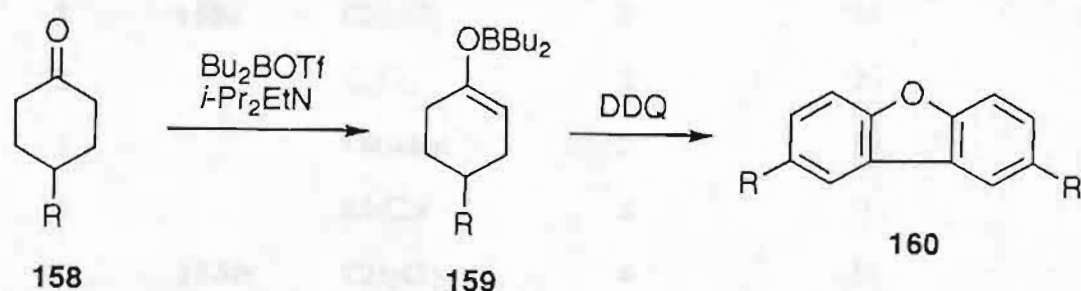


Figure 9-1.

First, the reaction of 1-(4-*tert*-butylcyclohexenyl)oxydibutylborane (**159a**) with DDQ was examined (Scheme 9-1). Vinyloxyborane **159a**, generated from the reaction of 4-*tert*-butylcyclohexanone (**158a**) (1.0 mmol) with dibutylboryl trifluoromethanesulfonate (triflate) (1.0 mmol) and diisopropylethylamine (1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.1 ml) *in situ*, was treated with DDQ (1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (13.3 ml) at room temperature for 1 h under nitrogen. 3,6-Di-*tert*-butyldibenzofuran (**160a**) was obtained in 29% yield together with large amounts of decomposed materials. Other compounds such as carbon-oxygen adduct, carbon-carbon adduct, or 4-*tert*-butylcyclohexenone were not detected. No reaction was

observed when ketone **158a** was treated with DDQ in  $\text{CH}_2\text{Cl}_2$  at room temperature for 1 h in the absence of dibutylboryl triflate and diisopropylethylamine.



a; R = *tert*-Bu, b; R = H, c; R = Me

Scheme 9-1.

When 2.0, 3.0, and 4.0 equiv. of DDQ were employed, the yields of **160a** were 32, 34, and 23% yields, respectively. The reactions using various solvents were examined using 3.0 equiv. of DDQ. The results are summarized in Table 8-1. The use of less polar solvents such as  $\text{CH}_2\text{Cl}_2$  or  $\text{C}_6\text{H}_6$  showed better results. Similarly, vinyloxyboranes **159b** and **159c** reacted with DDQ to give the corresponding dibenzofurans **160b** and **160c** in low yields, respectively (entries 5 and 6). On treatment of the other vinyloxyboranes derived from 2-methyl-, 3-methyl-, and 3,5-dimethyl-substituted cyclohexanones with DDQ, complete decomposition was observed.

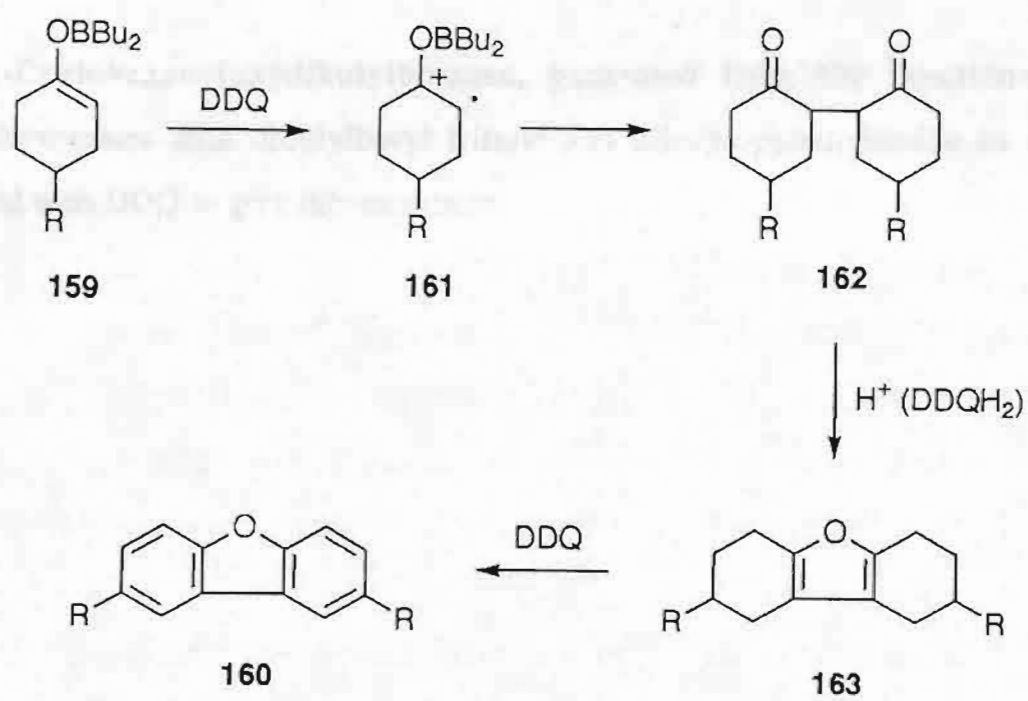
Table 8-1. The Reactions of Vinyloxyboranes Derived from Ketones **158a-c** with DDQ in Various Solvents

Entry	Ketone	Solvent	Time / h	Yield of <b>160</b> (%) <sup>a)</sup>
1	<b>158a</b>	CH <sub>2</sub> Cl <sub>2</sub>	2	34
2		C <sub>6</sub> H <sub>6</sub>	2	26
3		Dioxane	2	19
4		MeCN	2	10
5	<b>158b</b>	CH <sub>2</sub> Cl <sub>2</sub>	4	11
6	<b>158c</b>	C <sub>6</sub> H <sub>6</sub>	4	8

a) Isolated yields.

Dibenzofuran (**160**) could be formed by the mechanism as shown in Scheme 9-2. The first step is a SET process from vinyloxyborane (**159**) to DDQ. The resulting cation radical **161** would undergo dimerization to yield **162**. Acid-catalyzed ring closure of **162** by DDQH<sub>2</sub> probably gives octahydrodibenzofuran **163**.<sup>4)</sup> Dehydrogenation of **163** by DDQ leads to dibenzofuran **160**. From the reaction of vinyloxyborane **159a** with DDQ in CH<sub>2</sub>Cl<sub>2</sub> for 10 min, compound **163a** was isolated in 16% yield. Compound **163a** was also converted into **160a** smoothly under the conditions employed.





Scheme 9-2.

## Conclusions

1-Cyclohexenyloxydibutylboranes, generated from the reactions of cyclohexanones with dibutylboryl triflate and diisopropylethylamine *in situ*, reacted with DDQ to give dibenzofurans.

## Experimental

Column chromatography was performed on silica gel (Wakogel C-200).  $\text{CH}_2\text{Cl}_2$ ,  $\text{C}_6\text{H}_6$ , and MeCN were distilled over  $\text{CaH}_2$ . Dioxane was refluxed with sodium for 1 day and distilled. DDQ was recrystallized from benzene-hexane. IR spectra were determined on a Jasco IRA-2 or a Hitachi I-3000 spectrophotometer.  $^1\text{H}$  NMR spectra were determined on a JEOL JNM-FX 90Q (90 MHz) spectrometer using  $\text{Me}_4\text{Si}$  as an internal standard. Dibenzofuran **160b** was identified by comparison of the IR and  $^1\text{H}$  NMR spectra with those of the commercially available sample.

### General Procedure for the Reactions of Vinyloxyborane **159** with DDQ.

To a solution of diisopropylethylamine (0.185 ml, 1.0 mmol) and dibutylboryl triflate (1.0 M solution in  $\text{CH}_2\text{Cl}_2$ ) (1.0 ml, 1.0 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (0.9 ml) was added 4-*tert*-butylcyclohexanone (**158a**) (154 mg, 1.0 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (1.2 ml). After 15 min, DDQ (681 mg, 3.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (13.3 ml) was added. After stirring at room temperature for 1 h, the mixture was filtered, and the filtrate was extracted with  $\text{CH}_2\text{Cl}_2$ . The extracts were washed with water, dried, and evaporated and the residue was chromatographed on silica gel with hexane to give 3,6-di-*tert*-butyldibenzofuran (**160a**) (49 mg, 34%).

**160a**; colorless needles; IR (KBr) 2960 ( $\text{CH}_3$ ), 1482, and 822  $\text{cm}^{-1}$  (Ar);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 1.40 (18H, s,  $\text{CH}_3$ ) and 7.44-7.90 (6H, m, ArH).

**160b**; colorless needles; IR (KBr) 3100, 1600, 1480, and 740  $\text{cm}^{-1}$  (Ar);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 7.23-7.64 (6H, m, ArH) and 7.89-8.00 (2H, m, ArH).

**160c**; colorless needles; IR (KBr) 3030 (Ar), 2920, 2860 ( $\text{CH}_3$ ), 1618, 1480, and 817  $\text{cm}^{-1}$  (Ar);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.49 (6H, s,  $\text{CH}_3$ ) and 6.95-7.80 (6H, m, ArH).

**163a**; colorless oil; IR (neat) 2956, 2868, and 1474  $\text{cm}^{-1}$  ( $\text{CH}_2$  and  $\text{CH}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 0.88 (18H, s,  $\text{CH}_3$ ) and 1.05-2.20 (14H, m, CH and  $\text{CH}_2$ ).



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## Chapter 10. Summary and Conclusions

In this work, the author devised the several reactions using DDQ. The main part of this work is concerned with the protection of the functional groups and the deprotection of the protecting groups using DDQ. In Chapters 2-4, three new reactions catalyzed by DDQ, *i.e.*, tetrahydropyranylation of alcohols, deprotection of acetals and silyl ethers, were described. In Chapter 5, it was shown that the deprotection reactions were catalyzed by various  $\pi$ -acceptors as well as DDQ. Furthermore, a possible mechanism for the reactions was proposed. The deprotection of these protecting groups was catalyzed by acidic materials generated from the methanolysis of acceptors. In Chapter 6, the deprotection of 1,3-dithianes using 1.5 equiv. of DDQ was reported. Selective cleavage reactions of 1,3-dithiane in the presence of 1,3-dithiolane or diphenyl dithioacetal were performed. The deprotection of 1,3-dithianes was explained by the SET mechanism. In Chapter 7, the unexpected formation of benzaldehydes by the reactions of dithioacetals derived from cinnamaldehydes with DDQ was described and a possible mechanism was proposed. In Chapters 8, the author reported the reactions of DDQ with heterocyclic compounds. The reaction of DDQ with 6-methoxy-3-methylbenzofuran gave carbon-oxygen adduct. On the other hand, the reactions of DDQ with indoles gave carbon-carbon adducts. Benzofuran derivative and indoles afforded the different types of adducts. In Chapter 9, novel dibenzofuran formation from the reactions of cyclohexenyloxydibutylboranes with DDQ was described.

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## List of Publications

- 1) K. Tanemura, T. Horaguchi, and T. Suzuki, 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone as a Mild and Efficient Catalyst for the Tetrahydropyranylation of Alcohols, *Bull. Chem. Soc. Jpn.*, **65**, 304-305 (1992).
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